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THE LOCALISATION OF PAIN ON THE BODY: AN EXPERIMENTAL ANALYSIS

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GENERAL INTRODUCTION

ABOUT THAT THING CALLED PAIN

THE BURDEN OF PAIN

Sooner or later, everybody experiences pain in his or her life. Its onset can be sudden (e.g. when hitting your toe at the kitchen table) or more gradual (e.g. when developing a migraine attack) and its intensity can be rather mild (e.g. when having a paper cut) to unbearable (e.g. when giving labor). Despite the fact that pain can be very heterogeneous, everyone seems to agree that the experience is unpleasant, more often than not accompanied by uncontrolled swearing, and that we need it to disappear as fast as possible. On the bright side, pain is also adaptive, urging us to escape threatening situations and protecting us from future harm. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual of potential tissue damage, or described in terms of such damage" (IASP, 2012). In normal situations, pain is caused by intense stimuli that might damage the body, and results from the activity of specific sensory receptors and sensory pathways called the nociceptive system. In a clinical context, pain can be reported while the nociceptive stimulus is no longer applied. Pain can then result from excessive nociceptive responses (i.e. nociceptive pain) or from structural or functional impairments of the nervous system (i.e. neuropathic pain). Pain can also be categorized based on its duration (King, 2009). In cases of acute pain, the experience of pain only lasts for a few moments up to several months, depending on the inciting event, and is generally easily treated. In other people, pain may occur intermittently or continue to be present for a longer period of time (i.e. minimum three or six months for the classification of chronic pain). In chronic pain patients, the intensity of the pain seems no longer in proportion with the inciting event and pain can even be present without tissue damage, causing it to be highly resistant against treatment (Serpell, Makin, & Harvey, 1998).

Chronic pain is one of the most prevalent, costly and invalidating health problems (Park & Moon, 2010). A European chronic pain survey assessed the prevalence of chronic pain in 46,394 adult respondents and established that about 19% experienced chronic pain from moderate to severe intensity (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006). On top of that, chronic pain affects individual factors, such as psychological well-being, disability and employment status, but also economic aspects of society, such as costs related to health care and work absenteeism (Breivik et al., 2006).

FROM A BIOMEDICAL TO A BIOPSYCHOSOCIAL PERSPECTIVE ON PAIN

The conceptualization of pain and its treatment have long been dominated by the biomedical perspective on disease and healthcare. In the biomedical model, disease was viewed as a set of deviations from the norm of measurable biological variables (Engel, 1977), and biological markers (e.g. blood pressure, biopsy) determined further medical treatment. As such, all symptoms – either physical, psychological or social – were regarded as irrelevant (i.e. exclusionism) or were explained by disordered somatic processes (i.e. reductionism). Related to this, a strict separation was believed to exist between mind and body. This mind-body dualism originated from the Cartesian model, formulated by Descartes in 1664, which states that mind and body are distinct in the causation and outcomes of disease. Concerning pain, it was believed that there was a direct relationship between tissue damage and pain. This idea was formulated in the *specificity theory*, which stated that there are receptors and associated sensory fibers that each respond to only one type of stimulus (e.g. nociceptive, mechanic, thermal) (Dubner, Sessle, & Storey, 1978). As such, the perception of pain was viewed as a purely mechanistic process, determined by the activation of a pain receptor, responding to tissue damage. The more damage, the more pain people would experience. Another theory, the *pattern theory,* stated that it was not the activation of specific receptors or pathways that elicited a pain experience, but the activation of a pattern of responses in afferent systems (Sinclair, 1955; Weddell, 1955).

Although these one-dimensional models were fit to explain and to provide treatment solutions for acute pain, they were not able to account for a number of observations. Related to pain, it was observed that pain could still exist after tissue healing or after amputation, that it could change over time and of location, that it could be alleviated by placebo procedures and that it could even be elicited by innocuous stimuli (Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Melzack, 2005). A classic example, reported by Beecher (1959), describes soldiers returning from battlefield who, despite extensive wounds, only barely realized that they were injured. Together, these observations indicated that existing theories proposing a one-to-one relationship between pain and tissue damage were not able to grasp the complexity of the pain experience.

In response, Melzack and Wall formulated the Gate Control Theory in 1965 in which an isomorphic relationship between pain and tissue damage was no longer recognized (Melzack, 1974; Melzack & Wall, 1965). It was stated that a mechanism in the dorsal horns of the spinal cord operates as a 'gate' that inhibits or facilitates nociceptive processing. According to the authors, the gate system can be activated by two separate mechanisms. On the one hand, peripheral afferent nerve activity can open the gate when nerve fibers are activated that respond to noxious stimuli, and can close the gate when nerve fibers are activated that respond to non-noxious stimuli. On the other hand, descending central pathways can modulate the transmission of nociceptive information at the spinal cord. As such, the perception of pain can be influenced by cognitive (e.g. catastrophizing) and affective (e.g. pain-related fear) factors through this central pathway. Moreover, pain might not even be perceived when the gate is closed. The gate control theory was highly influential in pain research, focusing not merely on sensory-discriminative aspects of pain (e.g. quality, intensity, duration), but also on cognitive-evaluative and motivational aspects, paving the way for a biopsychosocial perspective on pain (Dubner et al., 1978).

According to the biopsychosocial model, biological, psychological and social factors are inherent in the constitution and treatment of illness and, by extension, also of pain (Engel, 1977; Gatchel et al., 2007). The distinction between "disease" and "illness" is thereby essential within the biopsychosocial perspective. Whereas disease is generally defined as an "objective biological event" that involves disruption of specific body structures or organ systems caused by pathological, anatomical, or physiological changes, illness refers to a "subjective experience or self-attribution" that a disease is present, possibly associated with physical discomfort, emotional distress, behavioral limitations and psychosocial disruption. The equivalent of this distinction in pain research is the difference between nociception, i.e. the stimulation of nerve fibers that convey information about tissue damage, and pain, which refers to the subjective experience associated with the processing of sensory input, that is affected by multiple factors like prior learning history, appraisals, sociocultural environment, etcetera (Turk & Gatchel, 2002). As such, the biopsychosocial model implies that the relationship between tissue damage and pain is variable and multidimensional. Moreover, according to this perspective, pain is constituted as a result of a widely distributed neural network within the brain that includes perceptual, behavioral and homeostatic systems that respond to injury and chronic stress. A somewhat different approach was the operant-behavioral perspective of Fordyce, who associated pain with the presence of pain behaviors, serving as operants that are influenced its consequences and that are involved in the maintenance of suffering and disability in chronic pain patients. Although Fordyce recognized the role of sensory-physical, affective, and cognitive factors in the emergence and maintenance of pain, he primarily focused on operant-behavioral aspects. In contrast, proponents of a cognitive-behavioral perspective argued that sensory-physical, affective, behavioral and cognitive factors are interrelated and emphasized the importance of cognitive factors, such as beliefs about and meanings attributed to pain (Turk, Meichenbaum, & Genest, 1983).

Taken together, the biopsychosocial model has inspired a wealth of research on pain and is now recognized as the most heuristic approach to chronic pain (treatment) (Gatchel et al., 2007). Moreover, due to the increased interest in psychological aspects of pain, cognitive psychology found its way into pain research and provided some new and interesting insights in the study of pain.

A COGNITIVE APPROACH TO PAIN: THE RELATIONSHIP BETWEEN PAIN AND ATTENTION

Within a cognitive approach to (chronic) pain, several models were developed that described a close relationship between pain and attention. For example, the cognitive model of pain, formulated by Leventhal and Everhart (1979), described a pathway of processing steps between the nociceptive input and the perceptual output that operate in parallel to give rise to the sensory-discriminative aspects of nociception on the one hand, and the emotional experience on the other hand. The model predicted that both aspects of pain can be influenced separately by attention. The model of Price and Harkins (1992) placed the sensory-discriminative and emotional experience of pain in a sequential order but also presumed both aspects to be affected by attention processes.

Given the assumption of the close relationship between pain and attention, more models were developed that focused on the fact that pain processing takes part in a cognitive system that was thought to have limited capacity for processing sensory events (see for instance Broadbent, 1958), in order to prevent sensory overload and to select the most adaptive responses (McCaul & Malott, 1984). Hence, the idea grew that the perception of pain would be affected by the relative amount of attentional resources dedicated to nociceptive processing. As such, dedicating more attention to a painful experience would worsen the pain. Similarly, it was expected that directing attention away from pain (i.e. distraction), towards other attention-demanding cognitive tasks, would minimize the remaining capacity to process it and would therefore result in a less salient pain perception and better coping with pain.

The latter assumptions were integrated in the *neurocognitive model of attention to pain* (Legrain, Van Damme, et al., 2009) that describes the difference between top-down and bottom-up attention to pain (see Figure 1). *Top-down control of attention* refers to the fact that certain stimuli are voluntarily attended, for example, to maintain cognitive goals or actions. Two important concepts, related to top-down attention, are attentional load and attentional set. Attentional load is defined as the amount of attention a person invests in a task (Legrain, Van Damme, et al., 2009). It implies that when a large amount of attention is already invested in a task, less attention will remain to process other stimuli (Legrain, Bruyer, Guérit, & Plaghki, 2005). Attentional set means that stimuli that share a set of perceptual features with already attended stimuli (e.g. task-relevant stimuli) will capture attention more easily. According to the neurocognitive model of attention to pain, the attentional load and attentional set in a certain task or situation will modulate which stimuli are attended and stored in the working memory for further processing (Legrain, Van Damme, et al., 2009). For example, investing attention in a task unrelated to pain – i.e. increasing the attentional load – has shown to diminish pain (Bingel, Rose, Gläscher, & Büchel, 2007). In contrast, attentional capture of pain during a task was higher when being presented with task-irrelevant nociceptive stimuli that share perceptual features with task-relevant targets (cf. attentional set; Legrain et al., 2002). Moreover, expecting non-painful somatosensory stimuli to be painful even increased the attentional capture of these stimuli (Crombez, Eccleston, Baeyens, & Eelen, 1998).

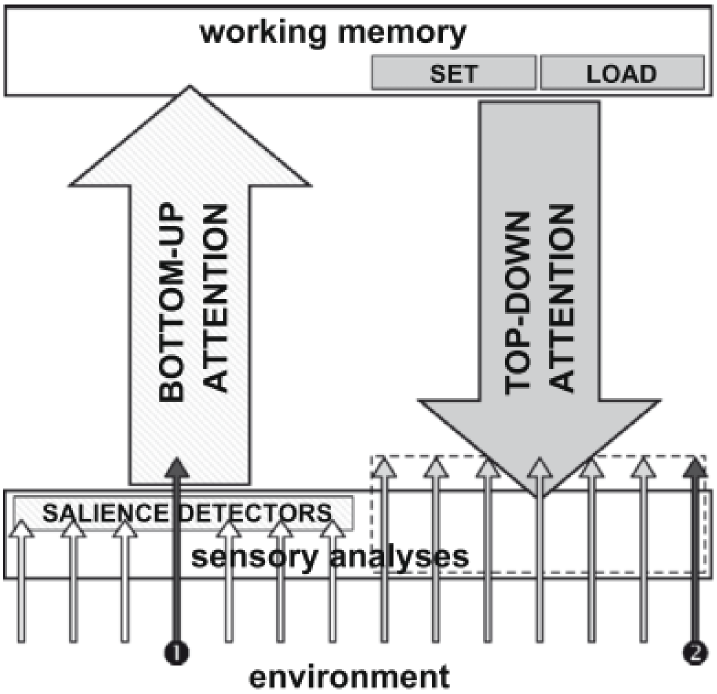

FIGURE 1. The neurocognitive model of attention to pain. Attention to pain is controlled by two different modes of attention. Bottom-up selection corresponds to the involuntary capture of attention by salient events, and can be modulated by top-down variables, i.e. voluntary processes that prioritize information relevant for current actions and goals. From Legrain et al. (2009)

In contrast, *bottom-up or stimulus-driven capture of attention* means that certain stimuli are prioritized in perceptual processing, based on their stimulus characteristics (e.g. intensity, novelty, sharpness of onset). These characteristics are often referred to as stimulus saliency. Saliency has been described as the ability of a stimulus to stand out, relative to neighboring stimuli (Knudsen, 2007; Yantis, 2008) and is, as such, always dependent on the way it contrasts surrounding stimuli (Knudsen, 2007; Yantis, 2008). Saliency is also dependent on past experiences in a way that stimuli that are novel or that deviate from what is expected from past experiences are proven to be more salient, and more able to capture attention (Crombez, Baeyens, & Eelen, 1994; Legrain et al., 2002; Legrain, Perchet, & García-Larrea, 2009). For example, it was found that applying a novel nociceptive stimulus, compared to a repeated nociceptive stimulus, during a visual cognitive task resulted in interference of that task as demonstrated by slower reaction times of the visual targets (Legrain, Perchet, et al., 2009).

Taken together, according to modern theories of attention and pain, the extent to which a nociceptive stimulus receives attentional resources, depends on its ability to stand out against other stimuli (bottom-up salience detection) and on its relative importance to a person's cognitive/behavioral goals (top-down selection) (Legrain, Mancini, et al., 2012). This close relationship between pain and attention fits well within a motivational perspective, in which pain is described as *"the archetypal warning of danger to an organism"* (Eccleston & Crombez, 1999) and attention (to pain) serves two seemingly opposite functions: (1) interrupting ongoing behavior and urging a person to escape a harmful situation, but on the same time (2) maintaining attention to meaningful goals without being distracted by other demands, such as pain (Eccleston & Crombez, 1999; Van Damme, Legrain, Vogt, & Crombez, 2010).

A FUNCTIONAL PERSPECTIVE ON PAIN: THE SALIENCE DETECTION THEORY

Given the alarm function of pain, it is reasonable to assume that especially nociceptive stimuli will be capable of attracting attention, interrupting ongoing activities and prompting appropriate behaviors to escape from bodily threat (Eccleston & Crombez, 1999; Pincus & Morley, 2001). Related to this, the *salience detection theory* (Legrain, Iannetti, Plaghki, & Mouraux, 2011; Legrain & Torta, 2015) gives a functional description of how nociceptive stimuli are automatically detected and prioritized in the stream of sensory information, based on their saliency. A series of studies (Liberati et al., 2016; Mouraux, Diukoca, Lee, Wise, & Iannetti, 2011; Mouraux & Iannetti, 2009; see Legrain, Iannetti, et al., 2011 for a more extensive overview) has shown that cortical activity in areas such as the insula, the anterior cingulate cortex and SII, that were considered specific for the processing of pain, could also be observed in response to non-nociceptive inputs, such as tactile, visual, and auditory stimuli. Based on these findings, these authors claim that the cortical activity, typically elicited by nociceptive stimuli, does not reflect specifically sensory processing of nociceptive inputs, nor specifically their transformation into pain, but instead the activity of a system involved in the prioritization of bodily-relevant stimuli, prompting behaviors related to homeostatic preservation (Legrain et al., 2011). Therefore, this cortical network is not only sensitive to nociceptive stimuli, but rather responds to stimuli from whatever sensory modality, as long they are sufficiently salient to stand out next to other stimuli. Nevertheless, it is stated that nociceptive stimuli might still in general be inherently more salient than non-nociceptive stimuli, due to the activity of some cutaneous receptors (e.g. TRPV1-receptors) that are selective to stimuli of high intensity, such as nociceptive stimuli (Belmonte & Viana, 2008). Based on these findings, a functional approach was taken on that describes pain as a *"warning signal allowing detection, localization and reaction against a stimulus potentially meaningful for the physical integrity of the body"* (Legrain & Torta, 2015). Three important functions are underlined by this definition of pain (see Figure 2): (1) selective attention, that is, detecting and orienting attention towards the most salient or relevant stimuli in order to prioritize its processing; (2) spatial perception, that is, localizing stimuli on the body and in the external space; and (3) action selection, that is, selecting and preparing the most appropriate (defensive) motor response. As these functions are not unique to pain, the focus is no longer on the perception elicited by nociceptive stimuli, but on the ability to detect changes in the environment that are behaviorally relevant or that can threaten the body (e.g. a wasp approaching the body), and to initiate appropriate action (e.g. moving away from the wasp) (Legrain & Torta, 2015). In the current PhD thesis, the main focus lies on one of these functions, namely: spatial perception of stimuli on and around the body.

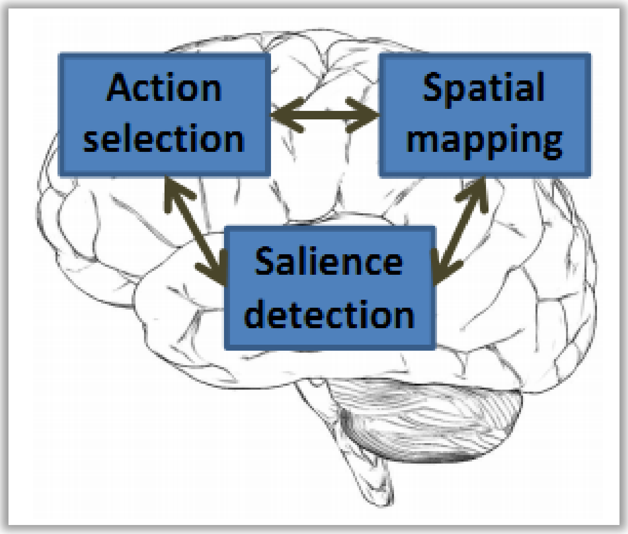

FIGURE 2. A functional approach to pain. Three functions are described that are important for the protection of the body's physical integrity: 1) salience detection and selective attention: detecting and orienting attention towards the most salient/relevant stimulus to prioritize its processing; 2) spatial mapping: localizing stimuli on the body and in external space; 3) action selection: selecting and preparing the most appropriate (defensive) motor response. Based on Legrain (2013).

SPATIAL PERCEPTION

In order to form an appropriate response to behaviorally relevant sensory events, the stimuli associated with this event need not only be detected and attended, but also localized with respect to the body. For example, when being attacked by a wasp, you will immediately swipe away the wasp or at least get away from it. Though this response might seem fairly automatic and straight-forward, it is the result of complex processes of mapping the sensory input. Such mapping processes are guided by internal reference frames that code the location of sensory events according to particular coordinates. These reference frames are believed to have the ultimate goal of guiding appropriate movements in response to sensory events (Colby & Goldberg, 1999; Fogassi et al., 1996).

Stimuli can be localized according to several regions of space (see Figure 3). First, a distinction can be made between stimuli in the personal space, referring to stimuli on the body surface, and stimuli in the external space, outside the body.

Whereas stimuli in the personal space are coded by somatosensory, but also vestibular and proprioceptive systems, stimuli in the external space are mainly coded by vision and hearing (Aglioti, Smania, & Peru, 1999; Avillac, Denève, Olivier, Pouget, & Duhamel, 2005; Galati, Pelle, Berthoz, & Committeri, 2010; Vallar, 1997). Further dissociations between reference frames can be made within the personal space (somatotopic vs. spatiotopic), within the external space (peripersonal vs. extrapersonal), and between an egocentric and allocentric frame of reference (cf. infra). Depending on the region of space in which stimuli have captured the attention, different frames of reference will be employed.

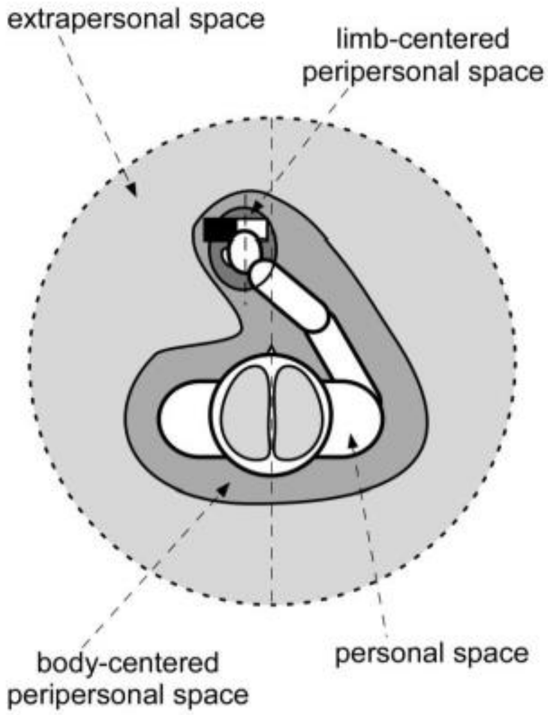

FIGURE 3. Different regions of space in which stimuli can be localized. The personal space corresponds to the space of the body itself. The peripersonal space refers to the space, closely surrounding the body, in which objects are within reach and can readily be manipulated. The peripersonal space can be centered on the body, with the sagittal body midline serving as coordinate for localizing stimuli, according to the left and right side of space (body-centered); or centered on the limb, using the limb itself as coordinate for localizing stimuli (limb-centered). The extrapersonal frame of reference corresponds to the space in which objects are beyond reach and is explored by eye movements and reaching movements of the limbs. From Legrain & Torta (2015)

SPATIAL REFERENCE FRAMES

EGOCENTRIC VERSUS ALLOCENTRIC

A first distinction can be made between an *egocentric* and an *allocentric* frame of reference (Galati et al., 2000, 2010; Paillard, 1991; Pani & Dupree, 1994; Zaehle et al., 2007). According to an egocentric reference frame, stimuli are represented relative to the body or to the body-parts. The location of stimuli within an egocentric reference frame, with the body regarded as the center of space, is therefore highly sensitive to body movements and requires constant re-mapping when the position of the body changes. In an allocentric frame of reference, stimuli are represented with respect to external objects or landmarks, independently from the position of the body.

SOMATOTOPIC VERSUS SPATIOTOPIC

A second distinction concerns the difference between a *somatotopic* and a *spatiotopic* frame of reference for coding the location of stimuli on the body surface (i.e. in the personal space). This partly depends on a direct correspondence between the spatial organization of skin receptors and their projection in specific and spatially segregated sub-groups of neurons in the primary somatosensory cortex (Narici et al., 1991; Penfield & Boldrey, 1937; Penfield & Rasmussen, 1950). This somatotopic organization only allows for the localization of stimuli on a certain part of the body, based on the usual position of that body-part in space. Yet, when having, for example, your arms crossed while being attacked by a wasp on your left hand - that is now positioned on the right side of space – the sole use of a somatotopic reference frame will code the position of the sting on the left side of the body, whereas the wasp having caused the sting is actually on the right side of space. In other words, a misconception will arise about the position of the wasp, as the somatotopic frame of reference does not take into account the relative position of the body-parts. Logically, this mislocalization of the threat would then in turn lead to misdirected defensive responses. Therefore, a spatiotopic frame of reference is also employed that provides a space-based representation of the body (Smania & Aglioti, 1995). The spatiotopic frame of reference codes the location of stimuli with respect to body, taking into account the current position of the body-parts, relative to each other and to the body midline, and relative to other external objects (Vallar, 1997).

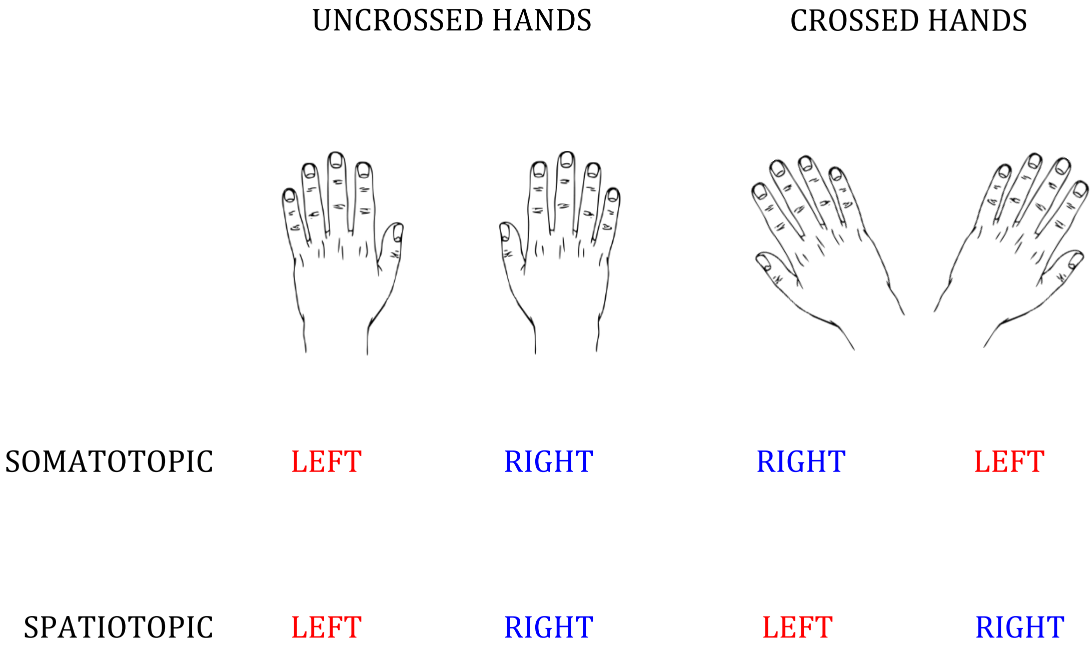

FIGURE 4. Graphical display of the dissociation between a somatotopic and spatiotopic frame of reference by comparing the direction of attention after being stimulated on one of the hands (e.g. tactile stimulus) during a crossed and uncrossed arm position. When arms are uncrossed, both a somatotopic and spatiotopic frame of reference will guide attention to the left side of space when a stimulus was given on the left hand, and to the right side when a stimulus was given on the right hand, making it impossible to dissociate between both reference frames. In contrast, when arms are crossed, a somatotopic frame of reference will still guide attention to the left side when the left hand is stimulated (vice versa for right hand stimulation), whereas a spatiotopic frame of reference will guide attention to the right side of space (i.e. the current location of the left hand) by integrating proprioceptive information on current limb position. From De Paepe et al. (2016b)

When aiming to dissociate between a somatotopic and spatiotopic reference frame, a crossed-hand procedure, comparing the direction of attention during crossed and uncrossed hand postures, has proven useful (see Figure 4). Evidence for dissociations between both reference frames has been found for the localization of tactile and nociceptive stimuli in healthy individuals. In a number of studies, participants' judgments of the temporal order of pairs of tactile or nociceptive stimuli, one applied on either hand, were impaired when participants' hands were crossed, compared to when they were uncrossed (Sambo et al., 2013; Shore, Gray, Spry, & Spence, 2005; Yamamoto & Kitazawa, 2001), also known as the 'crossed-hands deficit'. In addition, crossing the hands during nociceptive stimulation did even decrease intensity ratings of nociceptive and tactile stimuli and altered associated event-related potentials (ERPs) (Gallace, Torta, Moseley, & Iannetti, 2011). The 'crossed-hands deficit' and its possible impact on nociceptive processing is believed to originate from a mismatch between the location of the somatosensory stimuli within an arm-based (somatotopic) frame of reference and within a space-based (spatiotopic) frame of reference, possibly creating additional cognitive costs in realigning neural representations from different reference frames (Azañón & Soto-Faraco, 2008; Gallace, Soto-Faraco, Dalton, Kreukniet, & Spence, 2008; Torta et al., 2013; Yamamoto & Kitazawa, 2001).

A dissociation between a somatotopic and spatiotopic frame of reference was also found by investigating patients with somatosensory extinction following brain damage, using the crossed hands procedure. Extinction reflects a pathological condition characterized by an inability to detect a stimulus on the side of space contralateral to the damaged cortical hemisphere when a stimulus on the ipsilesional side is presented simultaneously (i.e. during double stimulation), while detection is intact for stimuli presented alone (i.e. during single stimulation). Smania and Aglioti (1995) asked patients to detect tactile stimuli (left, right or bilateral) on the hands, under crossed and uncrossed postures. Interestingly, impaired detection of tactile stimuli on the contralesional hand, as a result of somatosensory extinction, was more explicit when hands were uncrossed than when they were crossed. This indicates that these spatial deficits are not anchored to the contralesional hand, but to the contralesional side of space, thus being controlled by a spatiotopic, rather than a somatotopic frame of reference.

PERIPERSONAL VERSUS EXTRAPERSONAL

A final distinction is made between a *peripersonal* and an *extrapersonal* frame of reference, according to the region of external space in which stimuli are present (Halligan & Marshall, 1991). The peripersonal space is the region of space in which one can manipulate or grasp objects (Cardinali, Brozzoli, & Farnè, 2009; Rizzolatti, Fadiga, Fogassi, & Gallese, 1997) and is particularly relevant as it both codes the location of stimuli on the body (e.g. nociceptive stimulus from a wasp stinging you) and of stimuli closely surrounding the body (e.g. wasp buzzing around your head), both being potentially important for protecting the body (Maravita, Spence, & Driver, 2003). Therefore, the peripersonal space has been described as the region of space in which the body interacts with the outer world and is believed to be part of a cortical defense system, programmed to elicit defensive motor actions (Graziano & Cooke, 2006).

CROSSMODAL INTERACTIONS

Noteworthy, sensory events (e.g. bodily threats) are often not unimodal in nature but comprise stimuli from various sensory modalities (e.g. not only feeling the wasp but also seeing or hearing it). Integrating these multimodal sensory inputs might be advantageous to accurately localize the sensory event in external space and to form an appropriate response. Indeed, it has been argued that the crossmodal integration of stimuli from different sensory modalities results in a more coherent representation of external space (Spence & Driver, 2004a).

Research on crossmodal interactions has grown during the last decades. When studying crossmodal links in spatial attention, a distinction in experimental paradigms is made between exogenous attention (i.e. bottom-up, or captured 'reflexively' by salient events) and endogenous attention (i.e. top-down, or directed voluntarily), given the existing evidence on distinct neural substrates between the two forms of attention (Jonides, 1998; Klein, 1994). Another distinction concerns the difference between overt and covert orienting of attention. Whereas overt orienting is associated with receptor shifts (i.e. head, eye or hand movements) in the direction of the attended event, covert orienting is internal and therefore not observable without evaluating some sort of performance (Posner, 2007; Spence & Driver, 2004a).

CROSSMODAL INTERACTIONS IN EXOGENOUS ATTENTION

One of the best-established paradigms, designed to investigate crossmodal interactions in exogenous attention between the visual, auditory and tactile modalities is the 'orthogonal cueing paradigm' (Spence & Driver, 1994, 1996, 1997; Spence, Nicholls, Gillespie, & Driver, 1998). In an orthogonal cueing task, an abrupt cue is presented on a participant's left or right side, followed by a target from another modality on the same or the opposite location. In the prototypical example of the orthogonal cueing task, targets are presented on the thumb or index finger of each hand, holding a foam cube, whereby the index finger rests on top of the cube and the thumb on the bottom of the cube. Participants then make speeded discriminations of the targets on each side (e.g. up/down elevation discriminations with 'up' referring to a stimulus on the index finger and 'down' referring to a stimulus on the thumb), which are compared between trials in which cues and targets were presented on the same side (congruent or valid trials) versus the opposite side (incongruent or invalid trials). Two issues are important: (1) the cue is never predictive of the spatial location of the target; and (2) response mapping is orthogonal (e.g. up/down) to the direction of the cue (e.g. left/right), preventing the cue from causing any response biases (Filbrich, Torta, Vanderclausen, Azañón, & Legrain, 2016; Spence & Driver, 2004a). Even though the cues are spatially uninformative (i.e. non-predictive of target location), they are expected to attract attention to their location in a bottom-up, exogenous manner. The assumption is that, if a crossmodal link between two sensory modalities does exist, the 'capture' of attention towards the cued location would cause a corresponding enhancement in attentional processing of the target modality at the cued location, and would therefore result in increased performance on discriminating the targets. Using this paradigm, evidence has been found for crossmodal links between all combinations of visual, auditory and tactile stimuli (Buchtel & Butter, 1988; Butter, Buchtel, & Santucci, 1989; Farah, Wong, Monheit, & Morrow, 1989; Spence & Driver, 1997; Spence et al., 1998), with the exception of a non-existent effect of visual cues on auditory targets in covert attention (Buchtel & Butter, 1988; Spence & Driver, 1997).

CROSSMODAL INTERACTIONS IN ENDOGENOUS ATTENTION

A slightly adapted form of the orthogonal cueing task has been used to detect crossmodal interactions in endogenous attention (Spence & Driver, 1996). In general, participants are told that a target in one modality might be expected on one particular location (e.g. left hand). That way, participants' attention is mainly focused on that location in one modality. Elevation (up/down) judgments of the targets, but also of occasional distractors in another modality are then compared between the attended and unattended location. What is typically found is that participants' attention is not only shifted towards that location in the attended modality, but also in other modalities, even when there is no strategic advantage to it (Driver & Spence, 1998a). For instance, it was demonstrated in a series of experiments (Spence, Pavani, & Driver, 2000) that when a particular location is attended, due to the expectation of a tactile target on that location, visual attention is also shifted towards the attended location, irrespective of hand posture. Similarly, it was found that when participants expected an auditory target on one side, elevation (up/down) judgments were better for auditory stimuli at the attended location, compared to the unattended location, but visual judgments are better as well (Spence & Driver, 1996). Remarkably, the same was found in the opposite direction, that is, when targets were visual and distractors were auditory. This symmetry in the crossmodal links between vision and audition in endogenous attention, opposite to the asymmetry in exogenous attention, confirms that separate mechanisms underlie exogenous and endogenous (crossmodal) attention.

As mentioned earlier, localizing sensory events by integrating the multimodal sensory information that comes with such events is essential in establishing well-directed defensive motor responses. When aiming to localize the position of a sensory event, for example, the wasp that is still bugging you, (exogenous) crossmodal interactions between somatosensory (i.e. tactile or nociceptive) and visual are particularly relevant and have been studied extensively (for a review, see Spence & Driver, 2004a). As the focus of this PhD thesis lies on crossmodal interactions between vision and touch under different conditions, an overview will be given of evidence supporting a crossmodal link between vision and touch.

CROSSMODAL INTERACTIONS BETWEEN VISION AND TOUCH

Evidence for visuo-tactile interactions was retrieved primarily in the orthogonal cueing paradigm, as described earlier. For example, in a typical study, it was found that elevation (up/down) judgments of tactile targets on the hands were significantly better when an uninformative visual cue preceded a tactile target on the same hand, as opposed to the opposite hand (Spence et al., 1998). Moreover, it was shown that such visuo-tactile interactions hold under different hand postures (Driver & Spence, 1998a; Kennett, Eimer, Spence, & Driver, 2001). For example, when participants were asked to cross their arms over their body midline during an orthogonal cueing task, visual cueing effects on the processing of tactile targets completely reversed (Driver & Spence, 1998b). This proves that visuo-tactile interactions are not merely explained by a relatively larger hemispheric activation on the cued side (Kinsbourne, 1993) but rather remap across different postures – i.e. follow a spatiotopic, instead of a somatotopic frame of reference.

As it is unclear whether the effect of vision on touch is caused by a direct effect of vision of the proximity between visual stimuli and the body, or is mediated by proprioceptive information about such proximity, several experiments were conducted to dissociate the role of vision and proprioception in visuo-tactile interactions. For example, Làdavas et al. (2000) observed that the effect of visual stimuli on tactile perception was stronger when the hands were visible – and thereby also the proximity between the visual stimuli and the body - than when the hands were hidden from sight (i.e. when only proprioceptive information was available on the proximity between visual stimuli and the body). In addition, it was found that watching visual stimuli near fake (rubber) hands, aligned realistically, increased tactile elevation judgments on the real (unseen) hands to a larger extent, than when visual stimuli were watched without vision of the hands (real or fake) (Pavani, Spence, & Driver, 2000; Wesslein, Spence, & Frings, 2014). Notably, this effect was only found when participants experienced a sense of ownership towards the fake hands, that is, when the fake hands were incorporated into the body representation (Wesslein et al., 2014). As such, it seems that vision dominates proprioception in crossmodal interactions between vision and touch (see also Làdavas & Farnè, 2004).

Besides visual information about external events (e.g. an approaching wasp), visual information about the body itself can affect tactile processing as well. More specifically, it was found that simply viewing one's body increased tactile spatial acuity (Kennett, Taylor-Clarke, & Haggard, 2001), accelerated tactile reactions (Tipper et al., 1998), and modulated somatosensory-evoked potentials (Taylor-Clarke, Kennett, & Haggard, 2002). These effects have been labeled Visual Enhancement of Touch (VET) effects and have been attributed to back-projections from multimodal cortical areas, modulated by visual input (Taylor-Clarke et al., 2002).

VISUO-TACTILE INTERACTIONS IN THE PERIPERSONAL SPACE

Although the integration of multiple sensory modalities might seem fairly straightforward, complex processes are involved. The brain is computationally challenged to integrate information from different modalities that each cover a certain region of the space surrounding the body (e.g. vision in front of the body vs. audition also behind the body) and that each have a unique way of coding the location of stimuli in external space. More specifically, the stimulus properties of each modality that signals a common sensory event are very different at initial stages of sensory processing (Driver & Spence, 1998b). For example, visual stimuli are primarily coded retinotopically, auditory stimuli are tonotopic, and somatosensory stimuli are coded somatotopically (Driver & Spence, 1998b). Therefore, in order to integrate inherently different sensory inputs, the brain needs to remap the spatial coordinates of each modality into a common frame of reference.

The peripersonal frame of reference has been put forward as the frame of reference, responsible for the integration of multisensory information, especially visual and tactile. Indeed, the peripersonal space is characterized by a high degree of crossmodal interactions between vision and touch (Cardinali et al., 2009) that is less apparent at further distances from the body (Làdavas, di Pellegrino, Farnè, & Zeloni, 1998; Làdavas & Farnè, 2004). For example, when participants detected tactile stimuli on the hands while instructed to ignore concomitant visual stimuli near or far from the hands, cortical responses to tactile stimuli were of larger magnitude when visual stimuli occurred near the stimulated hand, as compared to when visual stimuli were delivered far from it (Sambo & Forster, 2009). Similarly, blink reflexes, elicited by electrical stimulation of the median nerve of the wrist (i.e. HBR for hand blink reflex), and described as a subcortical, defensive response, was enhanced when the stimulated hand was inside the peripersonal space (Sambo, Forster, Williams, & Iannetti, 2012; Sambo, Liang, Cruccu, & Iannetti, 2012).

Evidence for a peripersonal frame of reference in humans was also found in experiments studying extinction in brain-damaged patients (Brozzoli, Demattè, Pavani, Frassinetti, & Farnè, 2006). As already mentioned, patients with extinction typically fail to perceive contralesional stimuli when those are presented concomitantly with stimuli in ipsilesional side (i.e. double stimulation), but are able to perceive them when those contralesional stimuli are presented in isolation (i.e. single stimulation). Interestingly, it was found that the extinction phenomenon can also occur when stimuli are presented in different modalities. For example, the presentation of a visual stimulus near the ipsilesional hand caused extinction of a tactile stimulus in the contralesional hand (di Pellegrino, Làdavas, & Farnè, 1997; Farnè, Pavani, Meneghello, & Làdavas, 2000; Làdavas et al., 1998). Moreover, this crossmodal extinction effect weakened when the distance of the visual stimulus to the hand was increased.

Remarkable evidence for a peripersonal frame of reference coding the position of visuo-tactile events comes from animal research. In the ventral premotor cortex and the ventral intraparietal sulcus of the monkey brain, bimodal visuo-tactile neurons were discovered that are activated, both in response to visual and tactile stimuli (Duhamel, Colby, & Goldberg, 1998; Graziano, Yap, & Gross, 1994; Graziano & Gross, 1993; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981a, 1981b; Stein, Meredith, & Wallace, 1993). These neurons were found to have both visual and tactile receptive fields (RFs) that are in approximate spatial register – i.e. neurons with a tactile RF on the hand would also respond to visual stimuli near that hand.

Moreover, the visual RFs followed the tactile RFs while moving the limbs (i.e. limb-centered), regardless of eye movements and visibility of the moving limb (Graziano & Gross, 1993, 1995). As such, these studies provided the first evidence in non-human primates of spatial remapping of visuo-tactile events in a peripersonal frame of reference.

CROSSMODAL ATTENTION OR MULTISENSORY INTEGRATION?

When attempting to interpret exogenous crossmodal interactions, as discussed in the previous section, and when aiming to understand its underlying mechanisms, two distinct explanations arise. In cognitive psychology research, exogenous crossmodal interactions have traditionally been attributed to *crossmodal spatial attention*, that is, the ability to orient towards a common external source across several modalities (Spence, 2010; Spence & Driver, 2004b). At a cortical level, this would mean that when a stimulus in one modality arises, supra-modal brain regions turn on a metaphorical spotlight on the region of space in which this stimulus finds itself, thereby also prioritizing other stimuli – possibly from another modality – that are present on that location. Another mechanism is possible, however, related to the discovery of bimodal neurons in monkeys (e.g. Graziano et al., 1994; Graziano & Gross, 1993, 1998; Stein et al., 1993). These neurons displayed increased activity when a visual and a tactile stimulus were in approximate spatial register and were occurring very close in time. Although evidence for bimodal neurons with visual and tactile receptive fields has only been found in monkeys, using single-cell recordings, a similar mechanism might operate in humans (e.g. see Lloyd, Shore, Spence, & Calvert, 2003; Macaluso & Driver, 2001). It is then assumed that, through feed-forward projections from unisensory brain regions, multisensory areas respond to the concurrent presence of stimuli from different modalities. This *multisensory integration* account implies that stimuli from different modalities need to be present concurrently, in order to create crossmodal effects, whereas according to the crossmodal attention account, a stimulus (or cue) in one modality can on itself trigger crossmodal effects through the activation of supramodal brain regions (see Spence & Driver, 2004a).

Even though evidence has been found for both explanations, although for the multisensory integration explanation primarily in animals (cats and monkeys) (e.g.

Molholm et al., 2002), more specialized research, such as combined ERP and fMRI measures, lesion studies, transcranial magnetic stimulation (TMS) studies, and sophisticated single-cell recordings in animals, is needed to confirm the role of both explanations, or of their combination, in crossmodal interaction effects.

Following this introduction on human spatial perception, three specific contexts – each reflecting a research topic of this PhD thesis – will be discussed in which human spatial perception might take place and by which it might be affected.

SPATIAL PERCEPTION IN A DYNAMIC ENVIRONMENT

Unlike animal research, studies on crossmodal interactions in humans have primarily focused on the localization of static stimuli (e.g. light flashes emitted by light emitting diodes) in external space. Yet, (threatening) sensory events in real life are more often than not moving, possibly even approaching the body (cf. the approaching wasp). In line with this proposition, it was found that neural systems in the monkey brain, associated with the representation of the peripersonal space, display increased activity in response to moving stimuli, especially when they are approaching the body (e.g. Duhamel, Colby, & Goldberg, 1998; Fogassi et al., 1996; Graziano, Hu, & Gross, 1997).

In humans, clear effects have also been demonstrated for approaching – as opposed to receding – stimuli on tactile processing (Canzoneri, Magosso, & Serino, 2012; Cléry, Guipponi, Odouard, Wardak, & Ben Hamed, 2015; Gray & Tan, 2002; Huang, Chen, Tran, Holstein, & Sereno, 2012; Kandula, Hofman, & Dijkerman, 2015), especially when they are threatening (Carretié et al., 2009; de Haan, Smit, Van der Stigchel, & Dijkerman, 2016). As a result, crossmodal effects of visual approaching stimuli on tactile processing have been described as a visuo-tactile predictive mechanism, intended to detect and localize incoming threats or obstacles, in order to prepare defensive responses (de Haan et al., 2016; Kandula et al., 2015).

Although the abovementioned studies in humans provided interesting insights in the crossmodal effects of approaching visual stimuli on tactile and nociceptive processing, the manipulation of visual movement often lacks ecological validity.

Approaching and receding visual movements are mostly not even performed, but rather simulated by respectively increasing or reducing the size of stimuli on a computer screen. Therefore, the **first aim of this PhD thesis** was to investigate the effect of *in vivo* approaching visual stimuli on tactile processing in peripersonal space.

SPATIAL PERCEPTION IN THE ANTICIPATION OF PAIN

As mentioned earlier, an important purpose of spatial perception is to localize potentially relevant or threatening sensory events, in order to protect the body from harm. In that respect, many researchers have investigated perceptual processes in the context of bodily threat (Durnez & Van Damme, 2015; Koster, Crombez, Van Damme, Verschuere, & De Houwer, 2004; Lloyd, Morrison, & Roberts, 2006; Öhman, Flykt, & Esteves, 2001; Van Damme, Gallace, Spence, Crombez, & Moseley, 2009; Van Hulle, Durnez, Crombez, & Van Damme, 2015; Vanden Bulcke, Crombez, Durnez, & Van Damme, 2015). Traditionally, the effects of bodily threat on spatial attention have been investigated by showing participants threatening pictures and assessing the (facilitative) effect on the perception of other visual stimuli on or near the threatened body-part. Existing evidence indicates that visual processing is indeed enhanced near a body-part that is threatened by pictures showing threatening objects (e.g. a snake or a spider) (Koster et al., 2004; Van Damme et al., 2009). Moreover, it was found that even tactile processing is enhanced on a body-part that is presented with threatening pictures, compared to neutral pictures (Poliakoff, Miles, Li, & Blanchette, 2007; Van Damme et al., 2009). The latter studies serve as evidence for increased efficiency of visuo-tactile interactions in a threatening context, and fit well within a functional perspective on visuo-tactile interactions, facilitating the localization of incoming threats (cf. supra).

However, a methodological limitation in these studies is that pictures of threatening objects or situations do not pose a real threat to the body because they merely display a threatening context but do not involve actual pain, or the threat of it. Some researchers have overcome this issue by using cues that signal an impending painful or aversive stimulus (Durnez & Van Damme, 2015; Koster et al., 2004; Van Hulle et al., 2015; Vanden Bulcke et al., 2015; Vanden Bulcke, Van Damme, Durnez, & Crombez, 2013), and found that the resulting anticipation of pain captures attention and prioritizes the processing of tactile stimuli on that part of the body on which pain is expected. However, no direct evidence has yet been provided for increased efficiency of crossmodal interactions between vision and touch when actual pain is anticipated. Therefore, the **second aim of this PhD thesis** was to investigate whether pain anticipation facilitates crossmodal interactions between vision and touch.

SPATIAL PERCEPTION IN CHRONIC PAIN

Not only pain anticipation, but actual (chronic) pain can have an impact on spatial perception as well. For example, patients with fibromyalgia tend to be over-responsive to sensory information, especially pain- and body-related, compared to healthy individuals, indicated by lower pain thresholds and lower pain tolerance (Crombez, Van Damme, & Eccleston, 2005; McDermid, Rollman, & McCain, 1996). Moreover, although replication studies are needed, fibromyalgia may have an impact on the exact boundaries of the peripersonal space, consistent with the idea that these patients respond differently to stimuli that are far from the body, compared to healthy individuals (De Paepe et al., 2016b). These altered responses have been ascribed to processes of central sensitization (e.g. Desmeules et al., 2003), but have also been attributed to an over-attentiveness towards stimuli entering the peripersonal space, mediated by, for example, catastrophizing about threatening sensations (Legrain et al., 2011; McDermid et al., 1996).

Furthermore, chronic pain has been associated with distorted body (size) representations in several chronic pain conditions, such as chronic low back pain (Moseley, 2008), chronic pelvic pain (Haugstad et al., 2006), and complex regional pain syndrome (e.g. Lewis, Kersten, McCabe, McPherson, & Blake, 2007; Moseley, 2005; Peltz, Seifert, Lanz, Müller, & Maihöfner, 2011). Conversely, brain-damaged patients with somatoparaphrenia, that is, a decreased sense of ownership towards body-parts on the side of the body contralateral to the brain lesion, displayed reduced physiological responses to nociceptive stimuli, compared to a group of brain-damaged patients without somatoparaphrenia (Romano, Gandola, Bottini, & Maravita, 2014). Although these findings illustrate a close relationship between pain and spatial (body) perception, more research is needed to confirm and further elaborate this connection in other chronic pain populations (see Haggard, Iannetti, & Longo, 2013).

Although in healthy volunteers, recent evidence has suggested that nociceptive stimuli are integrated in a multisensory representation of body and space. A series of studies suggested that nociceptive stimuli can be mapped in a peripersonal frame of reference (De Paepe, Crombez, & Legrain, 2015, 2016a; De Paepe et al., 2016b; De Paepe, Crombez, Spence, & Legrain, 2014), similar to what was already found for tactile stimuli (e.g. Spence et al., 1998). More specifically, the perception of nociceptive stimuli on the hands was biased in favor of the hand that was cued by visual stimulus (light flash), but only when the visual stimulus was presented close to the hands (i.e. in peripersonal space), compared to far from the hands (i.e. in extrapersonal space) (De Paepe et al., 2016a, 2014). In addition, when hands were crossed, nociceptive perception was still biased towards the cued side of space, irrespective of arm posture (De Paepe et al., 2015), which implies that nociceptive stimuli are mapped in a spatiotopic or space-based frame of reference, rather than a somatotopic frame of reference (see also Gallace, Torta, Moseley, & Iannetti, 2011; Sambo & Iannetti, 2013). Moreover, crossmodal interactions between vision and nociception in the peripersonal space were not dependent on the proximity between visual stimuli and the trunk (body-centered), but on the proximity to the stimulated hand (limb-centered) (De Paepe et al., 2016b). Very recent studies have shown that the perception of visual stimuli can also be biased by nociceptive stimuli, depending of the relative proximity in space between the visual stimuli and the limb on which the nociceptive stimuli are applied (Filbrich, Alamia, Burns, & Legrain, 2015; Vanderclausen, Filbrich, Alamia, & Legrain, 2016). In sum, these studies are consistent with the idea that nociceptive stimuli can interact with visual stimuli in order to be integrated in a global representation of external danger, when visual stimuli appear close to the body (i.e. in peripersonal space), and that this peripersonal frame of reference takes into account the position of the body-parts in external space. At the cortical level, evidence for visuo-nociceptive interactions has been provided from animal studies in which neurons of the inferior parietal lobe have been shown to respond to both high intensity thermal stimuli and proximal visual stimuli (Dong, Chudler, Sugiyama, Roberts, & Hayashi, 1994). Evidence for such multisensory mechanisms in humans, although suggested by some studies (Liberati et al., 2016; Mouraux et al., 2011; Mouraux & Iannetti, 2009), is largely lacking.

Another well-known example of how nociceptive processing is affected by multisensory information is provided by studies having shown that pain can be reduced by simply viewing the body. For example, it was shown that viewing that part of the body that is administered a nociceptive stimulus reduces subjective pain ratings (Longo, Betti, Aglioti, & Haggard, 2009; Longo, Iannetti, Mancini, Driver, & Haggard, 2012; Valentini, Kock, & Aglioti, 2015) and increases pain thresholds (i.e. 'visual analgesia'; Mancini, Longo, Kammers, & Haggard, 2011; Martini, Perez-Marcos, & Sanchez-Vives, 2013) and the amplitude of nociceptive laser stimulus-evoked potentials (LEPs; Longo et al., 2009; Torta, Legrain, & Mouraux, 2015; Valentini et al., 2015), compared to viewing a non-body object. Moreover, increasing the perceived size of the hand by means of a magnification mirror further reduced the perception of pain (Mancini et al., 2011; Romano & Maravita, 2014) and nociceptive processing (Romano, Llobera, & Blanke, 2016), whereas reducing the perceived size of the hand resulted in the opposite effect. Although replication studies are needed to reconcile some conflicting findings (Beck, Làdavas, & Haggard, 2016; Torta et al., 2015), research has suggested an important link between body representation and pain sensation (e.g. see Longo et al., 2012). Evidence for such a link was also provided by studies on phantom limb pain. For example, simply watching the mirror reflection of the intact limb on the location of the missing amputated limb has shown to reduce phantom limb pain (e.g. Ramachandran, Rogers-Ramachandran, & Cobb, 1995). Conversely, absence of visual information in congenitally blind individuals, compared to late onset blind and sighted individuals, is related to higher pain sensitivity (Slimani, Danti, Ptito, & Kupers, 2014). These observations, being linked to cortical reorganization (e.g. Flor et al., 1995; Longo et al., 2012), indicate that pain perception and nociceptive processing depend on multisensory representations of the body and space.

COMPLEX REGIONAL PAIN SYNDROME

A remarkable case of impaired perception of the body and space is complex regional pain syndrome (CRPS). CRPS is a chronic, systemic disease, associated with a wide variety of symptoms, such as pain, changes in temperature and skin color, swelling and dystonia, typically affecting one limb (i.e. unilaterally) and generally resulting from minor trauma of the limb (e.g. sprain, fracture, surgery) (Marinus et al., 2011). Two types are generally distinguished, depending on the absence (CRPS, type I) or presence (CRPS, type II) of identifiable peripheral nerve injury (Bruehl et al., 1999). Notably, unilateral perceptual and motor dysfunctions have also been reported in CRPS patients, such as asomatognosia (i.e. feeling of strangeness/foreignness towards pathological limb), hypokinesia (i.e. smaller and less frequent movements), bradykinesia (i.e. slowness of movements), but also difficulties in mentally representing the pathological limb (Frettlöh, Hüppe, & Maier, 2006; Galer, Butler, & Jensen, 1995; Galer & Jensen, 1999; Lewis et al., 2010, 2007, Moseley, 2004, 2005; Schwoebel, Friedman, Duda, & Coslett, 2001). For example, CRPS patients were impaired in recognizing the affected limb (Moseley, 2004) and in estimating its size (Moseley, 2005), orientation (Schwoebel et al., 2001) and position (Lewis et al., 2010). Additionally, mislocalization problems of tactile stimuli have been reported, such as referred sensations and synchiria (i.e. stimulation on one hand evoking sensations in both hands) (Acerra & Moseley, 2005; Maihöfner, Handwerker, & Birklein, 2006; McCabe, Haigh, Halligan, & Blake, 2003), although the ability for higher order multisensory integration of body-relevant information remained intact (Reinersmann et al., 2013).

Interestingly, some of these perceptual deficits are similar to those observed in hemi-spatial neglect in post-stroke patients (Hasselbach & Butter, 1997). For example, Moseley, Gallace and Spence (2009) found that CRPS patients tend to bias the perception of tactile stimulation to the detriment of the stimulus applied on the pathological limb, and to the advantage of the stimulus applied on the opposite limb. However, this perceptual bias was completely reversed when patients’ arms were crossed over their body midsagittal plane. The perception of tactile stimuli was now biased at the advantage of the pathological limb. As such, the perceptual (neglect-like) bias was not anchored to the pathological limb (i.e. arm-based), but to the region of space in which it normally resides (i.e. space-based). The fact that the direction of the somatosensory perceptual bias is dependent on body posture indicates that the perceptual difficulties in CRPS patients are not caused by deficits in the peripheral coding and spinal transmission of somatosensory inputs (Schwenkreis, Maier, & Tegenthoff, 2009), but rather involve higher order cortical mechanisms (Janig & Baron, 2002). In other words, the difficulties in correctly perceiving tactile stimuli are not accounted by a somatotopic frame of reference, but by a spatiotopic frame of reference that takes into account the position of the body-parts. This is consistent with the idea that the symptomatology of CRPS is associated with cortical reorganization processes in brain regions concerned with body representations (Maihöfner et al., 2007; Maihöfner, Handwerker, Neundörfer, & Birklein, 2003; Schwenkreis et al., 2003). In line with this assumption, Moseley, Gallace and Iannetti (2013) found that impaired spatial (body) perception modulated the temperature of the limbs in CRPS patients, as well as tactile processing, spontaneous pain, and the sense of hand ownership.

Although the comparison between the symptomatology of CRPS and hemi-spatial neglect is still a matter of debate (see Legrain, Bultitude, et al., 2012; Punt, Cooper, Hey, & Johnson, 2013), investigating perceptual dysfunctions in CRPS patients might provide useful insights in the spatial mapping of chronic pain. However, besides the fact that evidence on the spatial mapping of touch and nociception in CRPS is still scarce, several conflicting findings are reported on the direction and exact nature of perceptual biases in CRPS (Reinersmann et al., 2012; Sumitani et al., 2007; Uematsu et al., 2009), but also on the generalizability to other chronic pain populations (e.g. see Frettlöh et al., 2006; Kolb, Lang, Seifert, & Maihöfner, 2012). For example, in contrast to what was found in phantom limb pain patients, pain complaints in CRPS patients *increased* when viewing an enlarged presentation of the affected hand and *decreased* when viewing a reduced presentation of the hand (Moseley, Parsons, & Spence, 2008). Recently, Reid et al. (2016) has attempted to overcome some of the conflicting findings in CRPS by explaining the heterogeneous symptomatology as a deficit in the integration of bodily representations with spatial processing, rather than a deficit in spatial processing *per se*. More specifically, it is argued that severe pain during the acute phase of CRPS would cause visuo-spatial representations of the CRPS-related space to become stronger, while limb mobility decreases and compensatory overuse of the healthy limb is observed. Although this might explain seemingly contradictory findings, such as shifted subjective body midline judgments towards the affected side (Sumitani et al., 2007), but impaired tactile acuity on the affected limb (Catley, O'Connell, Berryman, Ayhan, & Moseley, 2014), as well as unequal somatosensory representations of the affected and the healthy hand (Di Pietro et al., 2013), more research is needed to confirm these theoretical accounts.

The **third aim of this PhD thesis** was to gain more insight into perceptual deficits in CRPS patients by (1) replicating the findings of Moseley et al. (2009) on perceptual biases in CRPS under different postures, and (2) systematically comparing these to a group of non-CRPS pain controls.

AIMS AND RESEARCH PARADIGMS

In this PhD thesis, we aimed to investigate three research topics: (1) crossmodal interactions between vision and touch in a dynamic and ecologically valid context; (2) crossmodal interactions between vision and touch during pain anticipation; and (3) the spatial perception of touch in Complex Regional Pain Syndrome (CRPS).

Two experimental paradigms were used to target these objectives: the Temporal Order Judgment (TOJ) paradigm and the In Vivo Approaching Object (IVAO) paradigm. During the course of the PhD, the TOJ paradigm was first adapted to investigate crossmodal interactions between vision and touch during pain anticipation (**second objective**) and the spatial perception of touch in CRPS patients (**third objective**). After that, the IVAO paradigm was developed to investigate crossmodal interactions between vision and touch in a dynamic environment (**first objective**) and to extend the results on crossmodal interactions between vision and touch during pain anticipation (**second objective**).

TEMPORAL ORDER JUDGMENT PARADIGM

The theory of prior entry, as proposed by Titchener (1908), states that stimuli that are attended will come to consciousness prior to those stimuli that are unattended. The Temporal Order Judgment (TOJ) task (Pieron, 1952) was developed to measure this ‘effect of prior entry’ and has proven its usefulness in investigating crossmodal interactions in student and non-student populations (De Paepe et al., 2015, 2016a, 2014). In a typical TOJ task (Shore et al., 2005; Spence, Shore, & Klein, 2001), participants are presented with pairs of stimuli, interspersed by different time intervals (or SOAs for stimulus onset asynchronies). Participants are asked to judge which of the two stimuli of the pair has been perceived as being presented first. The mean SOA at which the participants judge the two stimuli as simultaneous is take as an index of participants’ perceptual bias denoting shifts in attention towards one of the two stimuli.

To investigate the second and third research objective, the TOJ task was adapted. In each trial of the TOJ task, participants were required to judge the temporal order of pairs of vibrotactile stimuli, presented one on either hand with SOAs varying between ±10, ±30, ±55, ±90 and ±200ms (negative sign indicating that the left hand was stimulated first). In the TOJ study targeting the **second objective** (i.e. crossmodal interactions between vision and touch during pain anticipation), a painful stimulus was alternately anticipated on one of the hands. In addition, vibrotactile stimulus pairs were briefly preceded by a light flash (LED), either near the hand that was stimulated first (congruent trials) or near the contralateral hand (incongruent trials). The light flashes could also be presented at a further distance from the participants hands (far cues vs. close cues). Importantly, as equal amounts of trials were used for congruent vs. incongruent conditions, the spatial congruency between the visual stimuli and the vibrotactile stimuli could not be predicted by the participants. Crossmodal interactions between vision and touch, near and far from the body, were inferred from the prioritization of tactile stimuli on the *cued* side, compared to the *uncued* side, and were compared between the hand on which *pain* was anticipated and the hand on which *no pain* was anticipated. In the TOJ study targeting the **third objective** (i.e. perceptual deficits in CRPS patients), pairs of vibrotactile stimuli were presented one on either hand, that is, on the pathological hand and the non-pathological hand. Shifts in somatosensory perception, due to CRPS, were assessed by comparing the prioritization of tactile stimuli between the pathological hand and the non-pathological hand.

One of the main outcome variables on the TOJ studies was the Point of Subjective Simultaneity (PSS). The PSS refers to the point at which participants perceive the two events (e.g. left hand first and right hand first) as equally often and corresponds to the SOA (ms) at which the two stimuli are perceived as simultaneous. As such, the PSS reflects shifts in the prioritization of tactile stimuli at one of either locations that was stimulated. An example of a graphical representation of the PSS is provided in Figure 5.

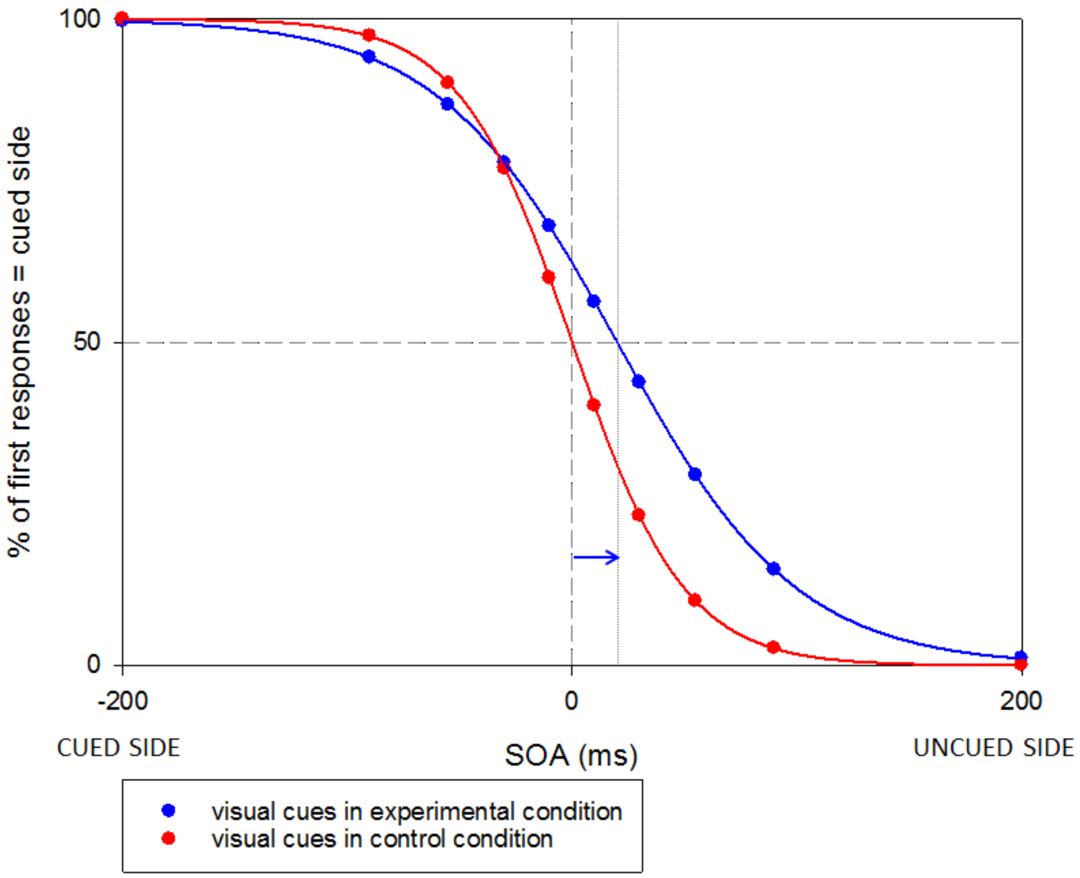

FIGURE 5. Graphical illustration of simulated TOJ data. The *x*-axis illustrates the SOAs and the *y*-axis represents the percentage of responses in which, in this example, the visually *cued* hand was perceived as occurring first. The PSS can be derived from the intersection point of 50% on the *y*-axis (*cued* and *uncued* hand reported first equally often) with the *x*-axis. In the absence of any attention shifts, the PSS (i.e. intersection with x-axis) will be zero (red line). A positive value indicates an attention shift towards the *cued* side (blue line), whereas a negative value indicates a shift towards the *uncued* side.

In our studies with healthy volunteers, crossmodal interactions between vision and touch would be reflected in a positive PSS (i.e. prioritization of tactile stimuli on the visually *cued* hand). Moreover, we might expect this PSS to be even larger when the visual cue was presented in peripersonal space, and/or when the *cued* hand was also threatened by the occurrence of painful stimuli. Similarly, heightened attention towards the pathological hand in chronic pain patients would cause the PSS to be positive (i.e. prioritization of tactile stimuli on the *painful* hand). In CRPS patients, we might expect the opposite, namely a prioritization of tactile stimuli on the unaffected hand (i.e. negative PSS).

Another parameter of the TOJ task is the just noticeable difference (JND), which is a standardized measure of the sensitivity of participants' temporal perception. The JND corresponds to the time interval that is needed between the two stimuli to acquire a 75% correct performance. No specific hypotheses were formulated in this PhD concerning the JND.

IN VIVO APPROACHING OBJECT PARADIGM

To target the **first research objective**, investigating crossmodal interactions between vision and touch in a dynamic environment, we developed a new paradigm, called the *In Vivo Approaching Object* (IVAO) task (see https://youtu.be/XzTFh4PLJOA for a demonstration video). In this task, participants are not presented with light flashes or other static visual stimuli that are often used in experiments, but with a neutral, pen-like object, held by the experimenter, that approaches the body. That way, visual stimuli resemble real-life situations (e.g. medical doctor testing somatosensory abilities of patients; patients becoming afraid when somebody approaches the painful body part), hence allowing swift translation to practical situations.

In each trial of the IVAO task, participants were approached towards their left or right hand with a neutral pen-like object, held by the experimenter. Once in the close proximity of the hand, a near-threshold vibrotactile stimulus was delivered to either the approached hand (congruent trials) or the contralateral hand (incongruent trials). Similarly to the TOJ task, the spatial congruency between the direction of the visual stimulus and the location of the vibrotactile stimulus could not be predicted by the participants. Tactile stimuli were just above or just below the perceptual threshold that was determined individually. Tactile Detection Accuracy (%), defined as the participants' ability to correctly detect and locate vibrotactile stimuli, was calculated as dependent variable. We hypothesized that the visual information resulting from an object approaching a body part would facilitate somatosensory processing on that body part (i.e. crossmodal visuo-tactile interaction). By changing the distance of the approaching movement to the participants' body (close vs. far), comparisons can be made between crossmodal interactions in extrapersonal and peripersonal space. Moreover, by changing the signal value of the pen-like object (e.g. by having it signal pain versus safety), crossmodal interactions can be evaluated during pain anticipation (**second research objective**).

OUTLINE DISSERTATION

PART I

The first research line of this PhD consists of several studies conducted on healthy volunteers and aims to investigate crossmodal interactions between vision and touch in a dynamic and ecologically valid context.

In **Chapter 1**, the In Vivo Approaching Object (IVAO) paradigm was piloted for the first time. We were interested in the effect of approaching visual cues, in peripersonal versus extrapersonal space, on tactile sensitivity. Participants were asked to detect and localize near-threshold vibrotactile stimuli on the hands, after being approached by a black pen, close to the hands or far from the hands. We evaluated whether tactile sensitivity was higher on the approached hand than on the contralateral hand and compared the size of these visuo-tactile interactions in peripersonal and extrapersonal space.

In **Chapter 2**, the IVAO task was employed to investigate the same research questions as in the previous chapter, provided some necessary methodological changes to the paradigm that was piloted in Chapter 1. In the first experiment, tactile sensitivity was compared between the visually approached hand and the opposite hand, but only in peripersonal space. In the second experiment, approaching movements were either close to the hands (i.e. in peripersonal space) or far from the hands (i.e. in extrapersonal space). Tactile sensitivity was compared between the approached and the opposite hand, and between close and far cues. Tactile sensitivity was expected to be higher for the approached hand, especially in peripersonal space.

In **Chapter 3**, the IVAO task was used to evaluate the role of vision, independent from proprioception, in visuo-tactile interactions. Participants' hand were hidden from sight and in half of the trials, two rubber hands were aligned realistically in front of the participants to elicit the illusion that the rubber hands were the real hands (i.e. Rubber Hand Illusion). Two target points above the real hands were approached, either in the presence or absence of the rubber hands. Tactile sensitivity was compared between the approached hand and the opposite hand, and between trials in which the rubber hands were present versus absent. Tactile sensitivity was expected to be higher for the approached hand, especially when rubber hands were present.

PART II

The second research line aimed to investigate crossmodal interactions between vision and touch during pain anticipation in a sample of healthy volunteers.

In **Chapter 4**, the IVAO task was adapted to evaluate visuo-tactile interactions when being approached by an object that signals imminent pain, compared to an object that signals safety. Two pens with different colors (blue and yellow) were developed to signal either the absence ("safety signal") or the possible occurrence ("pain signal") of painful stimuli on the approached hand. Tactile sensitivity was compared between the approached hand and the opposite hand and between trials in which the pen signaling pain versus the pen signaling safety had been used to approach participants. We expected tactile sensitivity to be higher for the approached hand, especially when it was approached by the pain signaling pen.

In **Chapter 5**, the TOJ task was used to investigate visuo-tactile interactions near a body-part that is threatened by imminent pain. Participants judged which of two vibrotactile stimuli, one applied to either hand, was presented first. Vibrotactile stimulus pairs were preceded by a visual cue (flash of light) on the same or the opposite side and either close to or far from the hands. In addition, one of the hands was alternately threatened by the occurrence of a painful electrocutaneous stimulus. We assessed shifts in attention towards the visually cued versus the uncued hand, depending on the location of bodily threat, and compared these between near and far space. Attention shifts were expected in the direction of the visual cues, especially when pain was anticipated.

PART III

The third research line includes a TOJ study in which perceptual deficits are evaluated in CRPS patients and compared to patients with non-CRPS chronic pain.

In **Chapter 6**, the presence of perceptual deficits was assessed in a population of CRPS patients and compared to two groups of non-CRPS chronic pain patients, namely: unilateral wrist pain patients and unilateral shoulder pain patients. Moreover, it was tested whether shifts in somatosensory perception were dependent on a somatotopic or rather spatiotopic representation of space. Participants judged the temporal order of pairs of vibrotactile stimuli, one applied to either hand, while having their arms in a normal, uncrossed, position or crossed over the body midsagittal plane. Shifts towards or away from the painful side were calculated and compared between the crossed and uncrossed posture. In the CRPS sample, a shift away from the affected hand was expected that reverses when arms are crossed (spatiotopic or space-based organization). In the non-CRPS samples, a shift towards the painful side was expected that is anchored to the painful limb, regardless of arm position (somatotopic or arm-based organization).

GENERAL DISCUSSION

Finally, in the **general discussion**, the main findings of all the studies are summarized, integrated and discussed. Furthermore, limitations to the studies, theoretical and clinical implications and suggestions for future research are formulated.

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PART I

CHAPTER 1

THE IN VIVO APPROACHING OBJECT PARADIGM: A PILOT STUDY[1]

ABSTRACT:

Research on crossmodal spatial attention has evolved and so have the research paradigms used to investigate this. Although the current paradigms on this topic have provided a great amount of relevant data on crossmodal interactions, they rarely resemble real-life situations. For example, static stimuli are most often used, whereas in real life, spatial attention and crossmodal processing include moving stimuli and moving body-parts. Based on these limitations, we developed a new paradigm, called the In Vivo Approaching Object (IVAO) paradigm. In this study, we piloted the IVAO paradigm (N = 29) to investigate crossmodal interactions between vision and touch near the body. Serving as visual cues, the experimenter approached a left or right target point near one of the participant's hands (= close cues) or further away from the hands (= far cues) with a neutral pen-like object. In half of the trials, this was immediately followed by a near-threshold vibrotactile stimulus (= target) on the same hand that was approached (unilateral congruent trials), on the opposite hand (unilateral incongruent trials) or on both hands (bilateral trials). In the remaining trials, no target was presented (catch trials). Tactile Detection Accuracy (TDA) was compared between congruent and incongruent trials and between close cues and far cues. We expected that visual cues would increase tactile sensitivity (TDA) near the body, as would be indicated by a higher TDA in congruent trials, compared to incongruent trials, especially for close cues. The results did not support our hypotheses: approaching the hand did not increase tactile sensitivity of the approached hand. However, some methodological aspects, including a low statistical power, might have affected the results and may need to be addressed in future studies. Besides these methodological issues, the IVAO paradigm and its potential applications are nevertheless promising.

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[1] Van der Biest, L., Legrain, V., Crombez, G. (unpublished manuscript). The In Vivo Approaching Object paradigm: a pilot study.

INTRODUCTION

The brain continuously receives information from the different senses about what is happening on and outside the body. To efficiently process this load of sensory information, the brain is able to detect and select stimuli that might be important to protect the body (Legrain, Iannetti, Plaghki, & Mouraux, 2011). However, stimuli originating from a certain external source (e.g. *seeing* a wasp attacking the body) are often associated with stimuli from other sensory modalities (e.g. *hearing* or *feeling* the wasp). Crossmodal studies have shown that these multimodal stimuli can be integrated when they are presented close to each other in space and time (Driver & Spence, 1998; Macaluso & Driver, 2001; Macaluso & Maravita, 2010; Spence & Driver, 2004). This integration of multimodal information provides a more coherent and stable representation of space and, as such, facilitates the localization of the sensory event with respect to the body (Driver & Spence, 1998).

Over the last decades, research on crossmodal spatial attention has grown substantially. At the same time, experimental paradigms have been developed. One of the most established paradigms for studying crossmodal interactions are spatial cueing tasks. For example, Driver and Spence (1998) have developed the 'orthogonal cueing' task, in which the effect of an unpredictive and task-irrelevant cue in one modality is measured on speeded discriminations of a target in another modality. Characteristic is that the direction of the cue presentation (e.g. left/right) is independent or orthogonal to the response mapping (e.g. up/down), and can therefore not bias decision making processes (Spence & Driver, 2004). For example, Spence, Nicholls and Gillespie (Spence, Nicholls, Gillespie, & Driver, 1998) found that such judgments of tactile targets were faster when uninformative visual and auditory cues were presented on the same side as the tactile targets. Another task is the temporal order judgment (TOJ) task in which participants judge the temporal order of pairs of stimuli, one applied to either location on the body (e.g. left/right hand). This task was developed to measure shifts in attention, based on the theory of prior entry that assumes that stimuli that are attended come into consciousness more quickly than unattended stimuli (Spence & Parise, 2010; Spence, Shore, & Klein, 2001). Recently, the TOJ paradigm was adapted to explore crossmodal spatial attention by adding unpredictive cues that precede the stimulus pairs. That way, it can be measured whether the perception of stimuli in one modality is biased by the presence of cues in another modality. Using this adapted TOJ task, it was found that temporal order judgments of pairs of nociceptive stimuli on the hands were biased in favor of the hand that was previously presented with an uninformative visual cue, especially when the cue was presented near the hands, as opposed to far from the hands, and irrespective of the relative position of the hand on which the nociceptive stimulus is applied (De Paepe, Crombez, & Legrain, 2015, 2016; De Paepe, Crombez, Spence, & Legrain, 2014)

An advantage of the above mentioned paradigms is that they allow strict experimental control over stimulus delivery. For example, visual stimuli are often presented as short flashes of light, transmitted from light emitting diodes (LEDs) that can be illuminated with a fixed timing, location and intensity. The downside, however, is that such experimental stimuli most often do not resemble real-life stimuli, impeding the generalizability of the results to real-life situations. Besides limitations in ecological validity, visual stimuli used in such tasks are mostly static. Yet, as the body and stimuli surrounding the body are often in motion, adopting dynamic visual stimuli seems essential to fully grasp the nature and mechanisms of crossmodal spatial attention. This has already been acknowledged in animal research, that has a longer history of using dynamic stimuli for studying crossmodal interactions (e.g. Dong, Chudler, Sugiyama, Roberts, & Hayashi, 1994; Graziano, Yap, & Gross, 1994).

Based on these limitations of current paradigms (lack of dynamic visual cues and limited ecological validity) we developed a new experimental paradigm, called the *In Vivo Approaching Object* (IVAO) paradigm. In the IVAO paradigm, first piloted in this study, near-threshold vibrotactile stimuli (= targets) were presented on the left and/or right hand and had to be detected and localized by the participant. Shortly preceding this, the experimenter, sitting across the participant, approached a left or right target point near the participant's hands (= close cues) or at a further distance from the hands (= far cues). It should be noted that *i)* the direction of the approaching movement was unpredictive of the target location; and that *ii)* the spatial congruency between cues and targets was evenly divided. Tactile detection accuracy (TDA) was calculated as a measure of tactile sensitivity and defined as the percentage of correctly detected and localized tactile targets. By comparing TDA between the *cued* and the *uncued* body-part, and between cues presented near or far from the hands, we were able to evaluate crossmodal links between vision and touch near the body (i.e. in peripersonal space). Based on earlier findings of visuo-tactile interactions in peripersonal space (Spence et al., 1998), we expected TDA to be higher for the *cued* body-part, especially when visual cues were presented near the hands.

METHOD

PARTICIPANTS

Thirty undergraduate students (age: *M* = 23.97; SD = 5.72; range = 16-48 years; 3 men; 2 left handed) took part in the experiment in exchange for a compensation of €10. Exclusion criteria were insufficiently corrected visual impairments, the self-report of current medical/psychiatric conditions or current medication intake affecting somatosensory sensitivity, and pain complaints on the upper limbs. None of the participants had to be excluded for these reasons. However, the experiment was discontinued for one participant who could not feel the tactile stimuli on the hands. As such, 29 participants were included for further analysis (age: *M* = 24.00; SD = 5.82; range = 16-48 years; 2 men; 2 left handed). The study was approved by the Ethics Committee of Ghent University. All participants gave their written informed consent.

STIMULI AND APPARATUS

Participants sat with their hands, palms down, resting on a table (see Figure 1). Four square metal plates (± 4cm^2) were attached to the table and used as electrical contacts. Two (*close*) plates were positioned between the thumb and index finger of each hand, 50cm apart from each other and about 30cm from the edge of the table (near the participant's trunk). The remaining two (*far*) plates were positioned on the same sagittal axes but at a distance of 50cm in front of the close plates. At a distance of 55cm in front of the edge of the table and ~35cm apart from each metal plate, a black fixation cross on the table prevented participants from shifting their gaze during the task. A chin wrest fixated the participant's head during the experiment. Participants wore headphones with continuous white noise (46dB) to mask auditory stimuli from the immediate environment. The experimenter sat across the participant at a distance of approximately 1 meter.

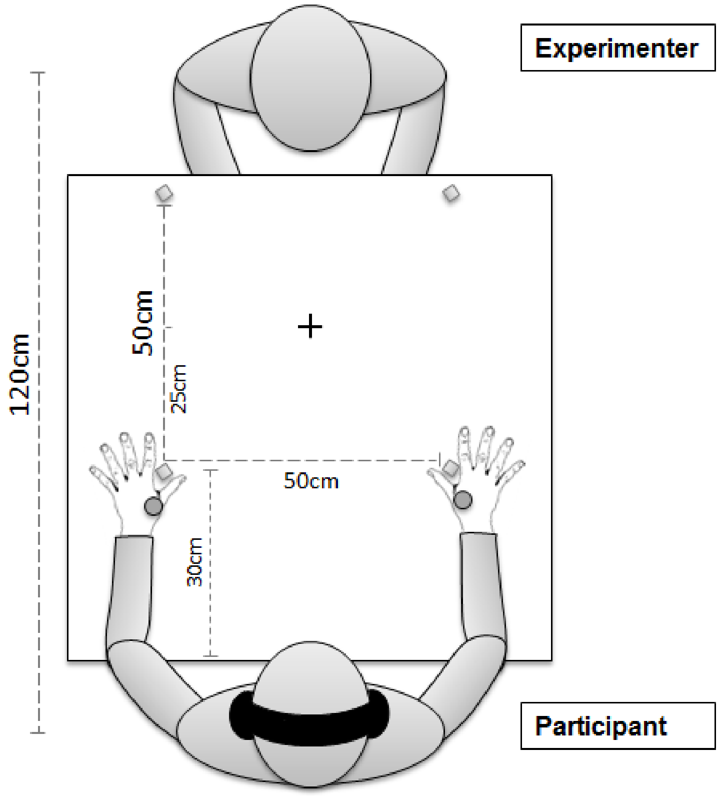

FIGURE 1. Experimental set-up of In Vivo Approaching Object IVAO task. Participants are seated across the experimenter with a *close* contact plate between either thumb and index finger and a *far* contact plate at a further distance.

VISUAL STIMULI

A pen-like object, held by the experimenter, served as a visual stimulus (see Figure 2). The experimenter (LVDB, female) moved the pen towards one of the close, or one of the far metal plates, tapped it and then moved back to the starting position of the movement. Depending on the plate that had to be approached (left or right), the arm closest to that side was used to perform the movement. The experimenter was trained to perform this movement in a standardized manner

(~1s approach and ~1s retraction). Tapping the plate triggered the delivery of a tactile stimulus (after a ~2ms time interval).

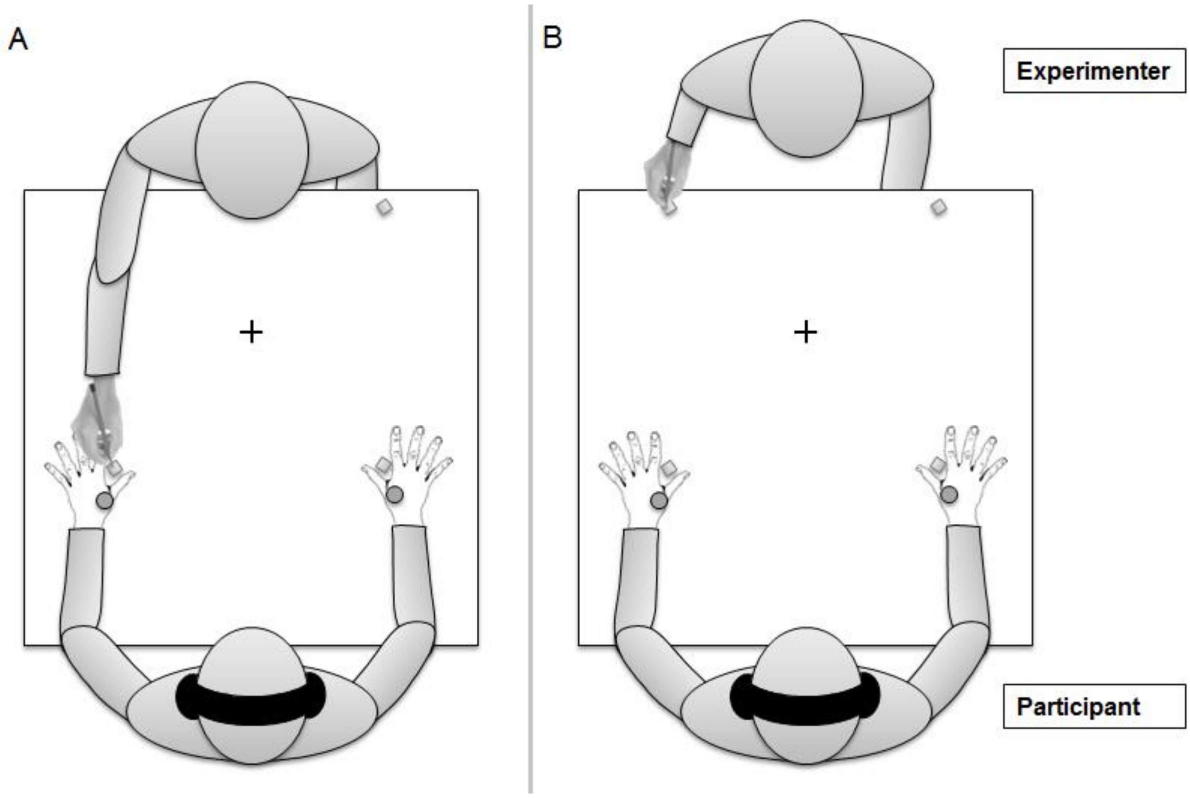

FIGURE 2. Illustration of approaching movement in close and far condition. During each trial, the experimenter approaches the participant's left or right side with the pen and taps the contact plate. The experimenter either approaches the *close* contact plates (Panel A, *close* condition) or the *far* contact plates (Panel B, *far* condition).

VIBROTACTILE STIMULI

Two magnet linear actuators (C-2 TACTOR, Engineering Acoustics Inc., Casselberry, Florida) were attached to the sensory territory of the superficial radial nerve of each hand and released vibrotactile stimuli (50ms duration; 50Hz). The actuators were driven by self-developed software and a controlling device that converted electrical signals (Watt) into oscillating movements of the actuators against the skin. The intensities of the vibrotactile stimuli were individually determined using an adaptive procedure determining the perceptual threshold. The procedure has been used in previous studies (Vandenbroucke, Crombez, Loeys, & Goubert, 2014; Vandenbroucke, Crombez, Harrar, et al., 2014). The procedure consisted of four independent yet randomly intermixed staircases of 20 trials (two series for each hand) randomly administered (80 trials in total). Each series had a starting value of 0.068Watt (W) for the first stimulus. The intensity decreased each time the participants reported feeling the stimulus, and increased when no sensation was reported. The perceptual threshold was determined for each hand, based upon the mean intensity of the last stimulus of each of the two series of that particular hand. *Sub-threshold* and *supra-threshold* values were calculated for each hand by respectively subtracting one eighth from the perceptual threshold value, or adding one eighth to it (see Press, Taylor-Clarke, Kennett, & Haggard, 2004).

SELF-REPORT MEASURES

Participants completed an anamnestic questionnaire (ad hoc developed) assessing socio-demographic characteristics, the Pain Grading Scale (PGS; Von Korff, Ormel, Keefe, & Dworkin, 1992), the Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995) and the Trait scale of the State-Trait Anxiety Inventory (STAI; Spielberger, 1987). The PCS and the STAI were included for a meta-analytic purposes and will not be discussed in this study. A series of self-report items was completed after each block to assess to what extent participants *i)* made an effort to perform the task; *ii)* were able to concentrate on the task; *iii)* felt tense/fearful during the task; *iv)* directed their attention towards the visual stimuli (approaching pen) and towards the tactile stimuli; *v)* perceived the tactile stimuli on the left and the right hand as intense; *vi)* found the pen threatening; *vii)* used the direction of the pen to predict the location (left/right) of the tactile stimuli; and *viii)* found the task meaningful (i.e. not having to guess). Each item was rated using a 11-point graphic rating scale (0 = “not at all”; 10 = “very much”).

PROCEDURE

After completing the questionnaires, participants were seated comfortably and received instructions about the staircase procedure. Headphones were turned on and participants were asked to place their chin in the chin wrest. In each trial, a visual stimulus (a letter X, 1000ms duration) appeared in the middle of a computer screen, placed in front of the participant, and was accompanied by a vibrotactile stimulus either on the left or right hand (position unknown to the participant). Participants verbally reported whether they had felt a vibrotactile stimulus ("yes" or "no"). Responses were manually inserted by the experimenter on a keyboard. When the staircase procedure was finished, the computer screen and the headphones were removed.

Before the experiment, participants were instructed to keep their hands still, not to touch the contact plates between their thumb and index finger and to fixate on the fixation cross during the task. Headphones were turned back on. In the *In Vivo Approaching Object* (IVAO) task, participants were required to detect a vibrotactile stimulus on the hands after being approached by the experimenter holding a pen. Each trial in the IVAO task started with the experimenter approaching the participant's left or right hand with the pen (visual cue), tapping one of the contact plates either near the hands (close visual cues) or far from the hands (far visual cues), and moving the pen back to its original position (near the experimenter's trunk). Simultaneously with the tapping, a sub-threshold or supra-threshold vibrotactile stimulus was presented on one or both hands in 50% of the trials (target trials). In the remaining 50% of the trials, no stimulus was presented (catch trials). The vibrotactile target could be presented on the same side as the visual cue (congruent unilateral target trials), on the opposite side (incongruent unilateral target trials), or on both sides (bilateral targets trials). Participants verbally responded whether they felt a tactile stimulus, and if so, on which hand (left, right or bilaterally). The four possible responses ("no sensation", "left sensation", "right sensation", "sensations on both sides") were manually inserted on the keyboard by the experimenter (0 = "no sensation"; 4 = "left sensation"; 6 = "right sensation"; 5 = "sensation on both sides"). Instructions about which hand to approach were visible on a computer screen in front of the experimenter but were masked from the participant's view. The experimenter, however, was blind as to which type of trial (congruent vs. incongruent) was running.

The design of the experiment is illustrated in Figure 3. In total, there were four experimental blocks of each 48 trials (192 trials in total). The distance of the visual stimuli alternated between blocks. Each block consisted of 24 catch trials, 8

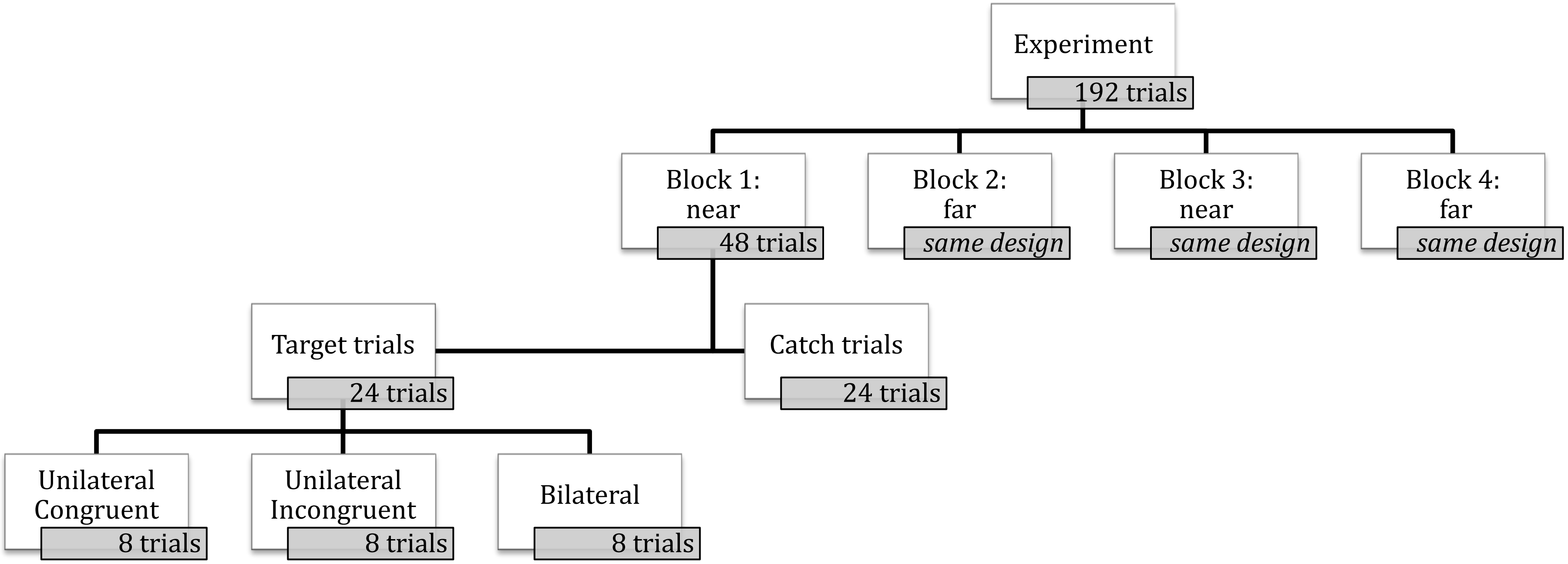

FIGURE 3. Experimental design of IVAO experiment. Intensity of the tactile stimuli was above (50%) or below (50%) the perceptual threshold.

congruent unilateral trials, 8 incongruent unilateral trials, and 8 bilateral trials. All four types of trials were presented randomly. Half of the target trials had a tactile stimulus of sub-threshold intensity (i.e. 12 trials), whereas the 50% had a tactile stimulus of supra-threshold intensity. Catch trials and bilateral trials were added to minimize strategic guessing and to maintain attention to the task. In sum, there were 8 observations (4 trials x 2 equivalent blocks) of congruent and incongruent unilateral trials for each intensity (sub- vs. supra threshold) of the targets and for each distance (near vs. far) of the visual cues. Participants completed the self-report items after each block.

ANALYSES

As we were interested in comparing tactile sensitivity of the *cued* and the *uncued* hand – i.e. the effect of spatial congruency between visual and tactile stimuli, bilateral and catch trials were discarded from the analyses. The outcome variable was the *Tactile Detection Accuracy* (TDA), defined as the percentage of trials on which participants correctly detected and localized the tactile targets. A repeated-measures Analysis of Variance (ANOVA) with within-subject factors *Intensity* (sub- vs. supra-threshold) of the tactile targets, *Congruency* (congruent vs. incongruent) and *Distance* (near vs. far) of the visual cues was performed on the TDA. The significance level was set at $p < 0.05$.

RESULTS

SELF-REPORT ITEMS

According to the self-report items administered after each block, participants made a large effort to perform the task (M = 8.41, SD = 1.07) and were able to concentrate well on the task (M = 8.48, SD = 0.93). They did not feel tense/fearful (M = 0.59, SD = 1.13) and found the task meaningful (i.e. not having to guess; M = 8.07, SD = 1.51). Concerning the stimuli used in the task, participants directed their attention to a large extent towards the tactile stimuli (M = 9.03, SD = 0.79), compared to the visual stimuli (i.e. the pen; M = 3.76, SD = 2.22). Participants reported not feeling threatened by the pen (M = 0.31, SD = 0.47), nor did they use the direction of the pen to predict the location (left/right) of the tactile stimuli (*M* = 0.49, SD = 0.75). The perceived intensity of the tactile stimuli was moderate and very similar between the left hand (*M* = 3.53, SD = 2.09) and the right hand (*M* = 3.69, SD = 2.23).

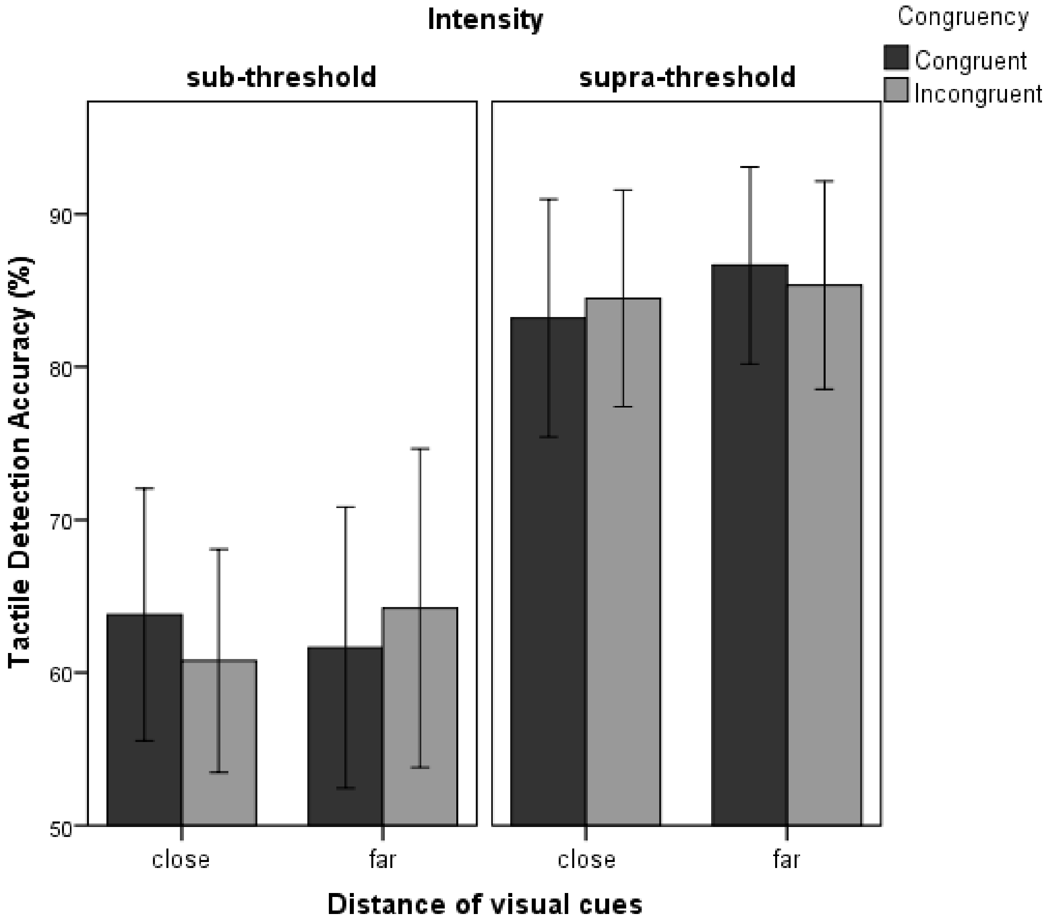

FIGURE 4. Tactile Detection Accuracy (%) in each condition. Error bars represent two standard errors of the mean (SEM)

TACTILE DETECTION ACCURACY

Mean TDA on unilateral trials was 73.76% (SD = 15.57). The repeated-measures ANOVA of *Intensity, Congruency* and *Distance* only revealed a main effect of *Intensity* ($F(1,28) = 69.95$, $p < 0.0001$), showing that TDA was higher for trials with supra-threshold targets (*M* = 84.91%, SD = 14.75), compared to sub-threshold (*M* =

62%.61, SD = 19.24) targets. There were no main effects of *Congruency* (*F*(1,28) = 0.002, *p* = 0.961) and *Distance* (*F*(1,28) = 0.38, *p* = 0.543). The expected interaction effect between *Congruency* and *Distance* was not significant (*F*(1,28) = 0.16, *p* = 0.690; Cohen's *d* = 0.18, CI = [-0.19:0.55]) (see Figure 4), although mean TDA in trials with sub-threshold targets and close cues was in line with what we expected, that is, TDA is higher for congruent trials (*M* = 63.79, SD = 22.25) than for incongruent trials (*M* = 60.78, SD = 19.69). There was also no interaction effects between *Congruency* and *Intensity* (*F*(1,28) = 0.004, *p* = 0.953) and between *Distance* and *Intensity* (*F*(1,28) = 0.17, *p* = 0.686). The three-way interaction between *Congruency, Distance* and *Intensity* was not significant (*F*(1,28) = 1.14, *p* = 0.294).

DISCUSSION

The aim of this study was to investigate crossmodal interactions between vision and touch in peripersonal space by means of the newly developed IVAO paradigm, characterized by dynamic and real-life resembling visual stimuli. We measured Tactile Detection Accuracy (TDA) on the *cued* and *uncued* hand and expected TDA to be higher for the *cued* hand (i.e. when visual and tactile stimuli were congruent) than for the *uncued* hand (i.e. when visual and tactile stimuli were incongruent), especially when visual cues were presented near the hands (i.e. in the peripersonal space).

Analysis of TDA in the different conditions did not reveal any significant effects, except that TDA was higher for trials with supra-threshold tactile targets than for trials with sub-threshold tactile targets. Therefore, no evidence was found to support our hypotheses. However, as the IVAO paradigm was only tested for the first time in this study, there are some methodological issues that might explain the lack of significant effects. First of all, compared to similar studies (Vandenbroucke, Crombez, Loeys, et al., 2014; Vandenbroucke, Crombez, Harrar, et al., 2014), TDA in congruent en incongruent trials was high, especially when the intensity of tactile targets was supra-threshold (*M* = 84.91%, SD = 14.75). This means that participants were already able to detect and localize the near-threshold tactile stimuli correctly in most of the unilateral trials, lowering the possibility of finding any effects of visual cueing. It could be that the tactile stimuli used in the experiment were still considerably higher than the perceptual threshold, as is indicated by the self-report data (i.e. perceived intensity of tactile stimuli was moderate). According to the *inverse efficiency effect* (Press et al., 2004; Stein & Meredith, 1993), the largest crossmodal interactions can be expected when stimuli are near the perceptual threshold. We suspect that during the staircase procedure, participants may have responded not to feel the tactile stimuli when they were not completely sure. We therefore suggest to modify the staircase instructions by emphasizing participants to reply “yes” (i.e. indicating that they feel the tactile stimulus) as long as they can differentiate its location (left/right). This minor adaptation could then result in a more accurate estimate of the perceptual threshold. Related to this, we propose to increase the proportion of sub-threshold trials (currently 50%) to 75% in future studies. Nevertheless, we want to keep supra-threshold trials to give participants a sense of mastery over the task. It may well be that participants will disengage from the task when feeling not able to master the task. Second, the statistical power might have been too low to detect significant results, due to the design of the study (i.e. only 8 observations in each condition). Therefore, we recommend to increase the proportion of congruent and incongruent trials in a way that all types of trials (unilateral congruent, unilateral incongruent, bilateral and catch trials) are divided equiprobably (see Vandenbroucke, Crombez, Harrar, et al., 2014 for a similar design). The total number of trials may also be raised to increase statistical power.

A particular limitation of the IVAO paradigm that needs consideration is the fact that the presentation of the visual cues (i.e. approaching movements) was not fully standardized. Although training of the experimenter improves the uniformity of the approaching movement, small variations in speed and smoothness never completely disappear. However, it is unlikely that this has affected the results because the order of the trials was randomized, and because the experimenter was blind as to which trials (congruent vs. incongruent) were running. Nevertheless, there are some aspects of the visual cues that may be improved. As can be seen on Figure 2, the distance between the experimenter and the participant was slightly smaller in the far condition, due to the experimenter reaching towards the close contact plates. Also, the constellation of the approaching movement was different in the far condition (experimenter reaching far) as compared to the far condition (experimenter not reaching at all). A better way may be to have the experimenter sitting at such a larger distance from the participant in the far condition, so that the approaching movement is similar in both conditions.

Although the IVAO paradigm was designed to investigate the effect of dynamic visual cues on tactile sensitivity, it may have further applications. First of all, other combinations of sensory modalities could be tested. For example, tactile stimuli could easily be replaced by nociceptive stimuli to evaluate crossmodal links between vision and nociception. Also, the impact of the person approaching the participant (e.g. male or female, doctor or not) could be subject of investigation. Similarly, the meaning of the pen could be varied by using different type of objects (e.g. syringe, cotton swab; see Sophie Vandenbroucke et al., 2014) or different colors that are linked to a certain outcome (e.g. pain vs. no pain). That way, visuo-tactile interactions could be investigated in the context of bodily threat.

In conclusion, we were not able to observe a crossmodal link between vision and touch in peripersonal space in this pilot study. However, low statistical power and low uniformity of the visual cues may have affected the results and may need improvement. Aside from these methodological issues, we believe that the IVAO paradigm can be employed to investigate a wide range of topics in crossmodal research. Moreover, the paradigm is innovative in adopting dynamic and real-life resembling visual stimuli.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest related to the present study.

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CHAPTER 2

WATCHING WHAT'S COMING NEAR INCREASES TACTILE SENSITIVITY: AN EXPERIMENTAL INVESTIGATION[2]

ABSTRACT

During medical examinations, doctors regularly investigate a patient's somatosensory system by approaching the patient with a medical device (e.g. Von Frey hairs, algometer) or with their hands. It is assumed that the obtained results reflect the true capacities of the somatosensory system. However, evidence from crossmodal spatial attention research suggests that sensory experiences in one modality (e.g. touch) can be influenced by concurrent information from other modalities (e.g. vision), especially near the body (i.e. in peripersonal space). Hence, we hypothesized that seeing someone approaching your body could alter tactile sensitivity in that body-part. In the In Vivo Approaching Object (IVAO) paradigm, participants detected and localized near-threshold vibrotactile stimuli administered on the left of right hand (= tactile targets). In Experiment 1, this was always preceded by the experimenter approaching the same (congruent trials) or the other (incongruent trials) hand with a pen (= visual cue). In Experiment 2, a condition was added in which a point further away from the hands (also left vs. right) was approached. Response Accuracy was calculated for congruent and incongruent trials (Experiment 1 & 2) and compared between the close and far condition (Experiment 2). As expected, Response Accuracy was higher in congruent trials compared to incongruent trials, but only near the body. As a result, evidence was found for a crossmodal interaction effect between visual and tactile information in peripersonal space. These results suggest that somatosensory evaluations – both medical or research-based – may be biased by viewing an object approaching the body.

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[2] Van der Biest, L., Legrain, V., De Paepe, A.L., Crombez, G. (2016). Watching what's coming near increases tactile sensitivity: An experimental investigation. *Behavioral Brain Research, 297,* 307-314.

INTRODUCTION

Imagine undergoing a medical examination, such as pressure algometry. Would your response be affected by seeing the doctor approaching you with the algometer? Health care providers often approach and touch the patient with testing devices such as von Frey hairs, algometers, or with their hands. These tests are often part of daily clinical practice but may also be part of specialized sensory evaluation such as the Quantitative Sensory Testing (QST) in patients with neuropathic pain. When these patients are approached and tested, they usually report upon the experience elicited by reporting the presence of the sensation, or rating the sensation (e.g. pain on a visual analogue scale). The assumption is that these reports reflect the capacity of the somatosensory system. However, such examinations do not consist only of somatosensory input. While approaching the body, also visual and possibly auditory information is present. It may well be that the integration of information from several perceptual modalities contributes to the experience of the patient.

This idea of crossmodal interactions has been the subject of extensive research in humans and animals (Driver & Spence, 1998a; Spence & Driver, 1997; Spence, Nicholls, Gillespie, & Driver, 1998). In a typical study of Spence et al. (Spence et al., 1998), participants were faster and more accurate in making speeded discriminations of tactile targets on the hand when a visual stimulus was presented on the same hand, as opposed to the other hand. Electrophysiological and neuroimaging studies have also confirmed crossmodal links in spatial attention (Calvert et al., 1999; Calvert, Campbell, & Brammer, 2000; Macaluso & Driver, 2001; Sathian, Zangaladze, Hoffman, & Grafton, 1997). For example, Sambo and Forster (2009) recorded somatosensory evoked potentials of increased magnitude when the tactile stimuli applied to one hand were presented concomitantly with a visual cue near that hand. Multisensory interactions have also been proposed for pain, which would facilitate the localization of painful stimuli in close proximity to the body (Haggard, Iannetti, & Longo, 2013; Legrain & Torta, 2015). De Paepe et al. (2014) have shown that judgment about the detection of nociceptive stimuli is facilitated by visual stimuli delivered close to the body part on which is applied the nociceptive stimuli.

It seems reasonable to hypothesize that the visual information resulting from an object approaching a body part in close proximity will facilitate the somatosensory processing of that body part. There is some evidence in support of this idea (e.g. Graziano & Gross, 1995), but no study has investigated visuo-tactile interactions in situations resembling clinical and/or QST practices. Therefore, we developed the "In Vivo Approaching Object paradigm", which mimics clinical examinations but also allows for experimental control over stimulus delivery. During each trial, a pen was directed by the experimenter towards a hand of the participant. Once in close proximity to the hand, a vibrotactile stimulus (at sub- or supra-threshold) was delivered to either the approached hand (congruent trials) or the other hand (incongruent trials). The participants' ability to accurately detect and locate the vibrotactile stimulus was measured. In Experiment 1, the pen was directed towards the proximal space of one of the hands. Experiment 2 extended Experiment 1 by also including a condition in which the object was directed towards a location at a further distance from the hands. It was expected that detection accuracy would be higher for congruent than incongruent trials, especially when the pen approached the proximal space of the hand, as opposed to a location at a further distance from it.

EXPERIMENT 1

METHOD

PARTICIPANTS

Thirty undergraduate students took part for course credits (age: *M* = 21.00; SD = 5.59; range = 17-43 years; 3 men; 5 left handed). Exclusion criteria were insufficiently corrected visual impairments, the self-report of current medical/psychiatric conditions, or current medication intake affecting somatosensory sensitivity. None of the participants had to be excluded. The study was approved by the Ethics Committee of Ghent University. All participants gave their written informed consent.

STIMULI AND APPARATUS

During the In Vivo Approaching Object (IVAO) task, participants were seated with their hands, palms down, resting on a table (see Figure 1). Two square metal plates (± 4cm^2) were used as electrical contacts. They were attached to the table, 50cm apart from each other and positioned between the thumb and index finger of each hand. The distance between the edge of the table – near the participant's trunk – and the plates was 30cm. At a distance of 55cm in front of the edge of the table and ~35cm apart from each metal plate, a black fixation cross was presented on the table to prevent participants from shifting their gaze during the task. The participant's head was fixed using a chin wrest. Headphones with continuous white noise (46dB) were used to mask auditory stimuli from the immediate environment. The experimenter was sitting on the other side of the table, at a distance of approximately 1 meter, facing the participant.

VISUAL STIMULI

A black pen was held by the experimenter and served as a visual stimulus. The experimenter (LVDB, female) held the pen in her left or right hand, and smoothly moved her arm towards one of the two metal plates near the participant's hands, and finally tapped the metal plate. She then moved back to the starting position of the movement. Depending on the plate that had to be approached (left or right), the arm closest to that side was used to perform the movement. Tapping the plate triggered the delivery of a tactile stimulus after a time interval of ~2ms.

VIBROTACTILE STIMULI

Two magnet linear actuators (C-2 TACTOR, Engineering Acoustics Inc., Casselberry, Florida) were attached to the sensory territory of the superficial radial nerve of each hand and released vibrotactile stimuli (50ms duration; 50Hz). The actuators were driven by a self-developed controlling device and software. The intensities of the vibrotactile stimuli were near the perceptual threshold, which was individually determined using an adaptive procedure. The procedure has been used in previous studies (Vandenbroucke, Crombez, Loeys, & Goubert, 2014; Vandenbroucke, Crombez, Harrar, et al., 2014). The procedure consisted of four

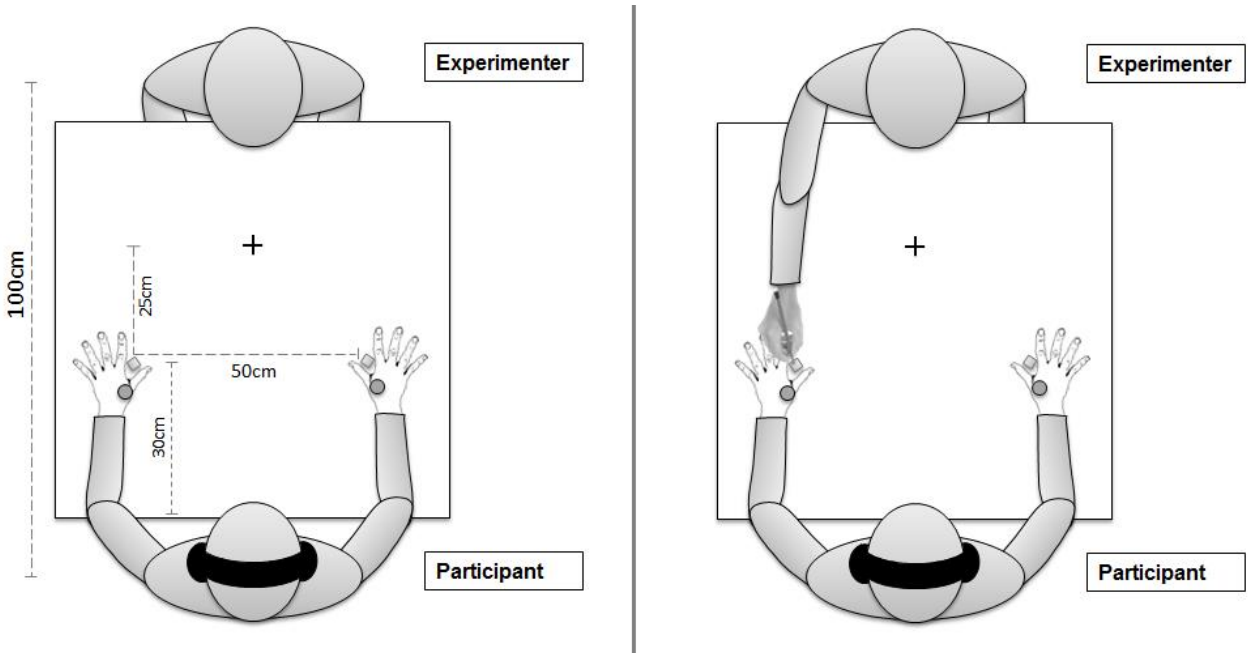

FIGURE 1. Experimental set-up of the IVAO task in Experiment 1. Left panel: Participants are seated across the experimenter with a *close* contact plate between either thumb and index finger. Right panel: during each trial, the experimenter approaches one of the participant's hands with the pen, taps the contact plate and returns to the starting position (see left panel).

independent yet randomly intermixed staircases of 20 trials (two series for each hand) randomly administered (80 trials in total). Each series had a starting value of 0.068Watt (W) for the first stimulus. The intensity decreased each time the participants reported feeling the stimulus, and increased when no sensation was reported. The perceptual threshold was determined for each hand, based upon the mean intensity of the last stimulus of each of the two series of that particular hand. *Sub-threshold* and *supra-threshold* values were calculated for each hand by respectively subtracting one eighth from the perceptual threshold value, or adding one eighth to it (see Press, Taylor-Clarke, Kennett, & Haggard, 2004).

SELF-REPORT MEASURES

Participants completed an anamnestic questionnaire (ad hoc developed) containing socio-demographic items and consisting of the Pain Grading Scale (PGS; Von Korff, Ormel, Keefe, & Dworkin, 1992), allowing the classification of participants as a function of experienced pain and disability during the last 6 months. Also, current treatment for medical or psychiatric conditions, medication intake and perceived health quality were assessed. Participants also completed the Dutch versions of the Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995) and of the Trait scale of the State-Trait Anxiety Inventory (STAI; Spielberger, 1987). The PCS and the STAI were included for a meta-analytic investigation on the role of individual differences in studies on this topic. Individual studies often lack the statistical power to reveal precise estimations of such effects, and hence these data will not further be discussed, but can be requested by addressing the authors.

After each block, a series of self-report items assessed to what extent participants made an effort to fulfill the task; were concentrated on the task; felt tense/fearful during the task; directed their attention towards the pen and the tactile stimuli; experienced the pen as threatening; and used the pen to predict the location of the tactile targets. Each item was rated using a 11-point graphic rating scale (0 = "not at all"; 10 = "very much").

PROCEDURE

Participants started with filling out the socio-demographic questionnaire, the PCS and the STAI, after which the staircase procedure followed. Participants were instructed to lay their arms on the table and to find a comfortable position by having the chin wrest and their chair adjusted. A computer screen was placed in front of the participant and instructions about the staircase procedure were given. Following this, the headphones were turned on and the staircase procedure started. First, a visual stimulus (a letter X, 1000ms duration) appeared in the middle of a computer screen, accompanied by a vibrotactile stimulus either on the left or right hand (position unknown to the participant). Participants verbally reported whether they had felt a vibrotactile stimulus ("yes" or "no"). Responses were manually inserted by the experimenter on a keyboard. When the staircase procedure was finished, the computer screen and the headphones were removed. Then, the experimenter calculated the sub- and supra-threshold intensities.

During the *In Vivo Approaching Object* (IVAO) task, participants were instructed to keep their hands in a way that each metal plate was positioned between thumb and index finger, and was not being touched (see Figure 1). Participants were also told to fixate the fixation cross during each block. Each trial started by the experimenter approaching the participant's left or right hand with the pen (visual cue), tapping the metal plate next to the hand, and moving the pen back to its original position (near the experimenter's trunk). The experimenter was trained to perform this movement in a standardized manner (~1s approach and ~1s retraction). Simultaneously with the tapping, a sub-threshold or supra-threshold vibrotactile stimulus on one or both hands was triggered in 75% of the trials (target trials). In the remaining 25% of the trials no stimulus was presented (catch trials). The vibrotactile target could be presented on the same side as the visual cue (congruent unilateral target trials), on the opposite side (incongruent unilateral target trials), or on both sides (bilateral targets trials). Participants verbally responded whether they felt a tactile stimulus, and if so, on which hand (left, right or bilaterally). The four possible responses, i.e. "no sensation", "left sensation", "right sensation", "sensations on both sides", were manually inserted on the keyboard by the experimenter (0 = "no sensation"; 4 = "left sensation"; 6 = "right sensation"; 5 = "sensation on both sides"). Instructions about which hand to approach were visible on a computer screen in front of the experimenter but were masked from the participant's view. The experimenter, however, was blind as to which type of trial (congruent vs. incongruent) was running.

The design of Experiment 1 is illustrated in Figure 2. A total of 256 trials was presented, divided across 4 blocks of 64 trials. Each block consisted of 16 catch trials, 16 congruent unilateral trials, 16 incongruent unilateral trials, and 16 bilateral trials. All four types of trials were presented randomly. The majority (75%) of the target trials had a stimulus of sub-threshold intensity (i.e. 36 trials), whereas 25% had a stimulus with an intensity slightly above the perceptual threshold (i.e. 12 trials). Supra-threshold targets were presented in order to provide participants a sense of mastery over the task. Catch trials and bilateral trials were added to minimize strategic guessing and to maintain attention to the task. In sum, there were 16 observations (4 trials x 4 blocks) per condition for supra-threshold tactile targets and 48 observations (12 trials x 4 blocks) per condition for sub-threshold targets. Participants completed the self-report items after each block.

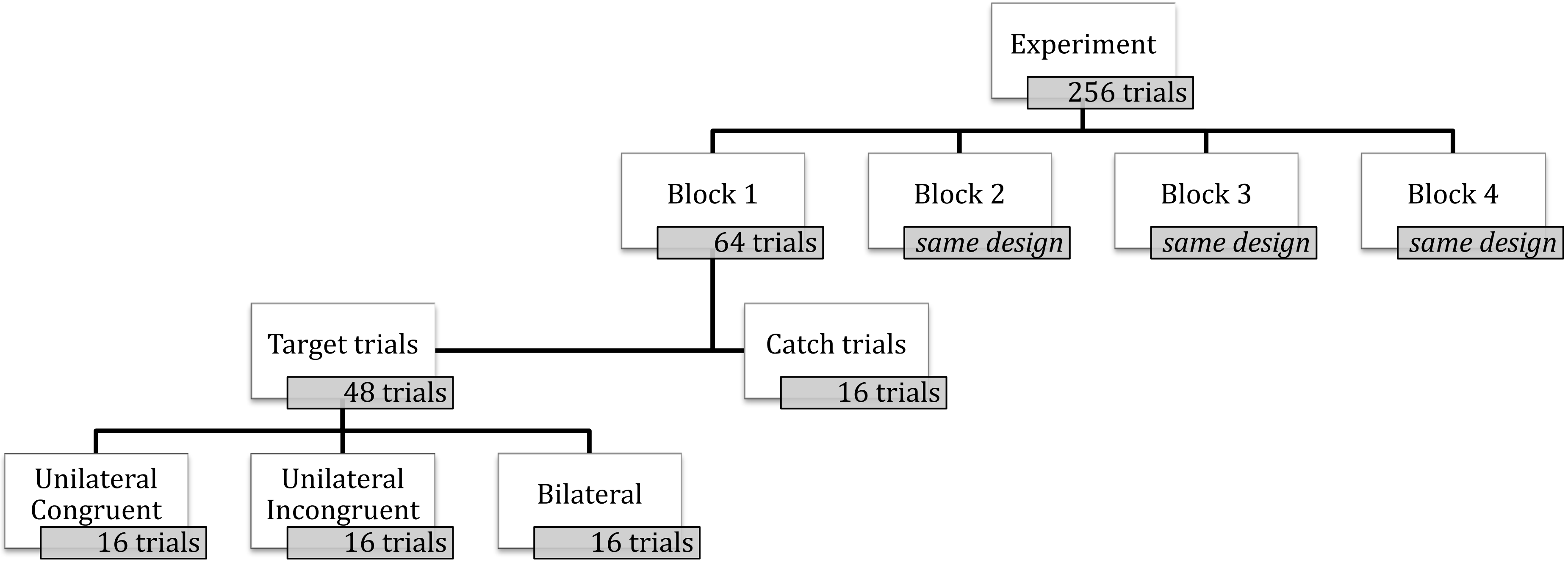

FIGURE 2. Experimental design of Experiment 1. Intensity of the tactile stimuli was above (25%) or below (75%) the perceptual threshold.

ANALYSES

Analyses were conducted on *Response Accuracy* (binomial: correct vs. incorrect) during the unilateral tactile targets. Catch trials and bilateral target trials were discarded. A response was considered as correct when the vibrotactile stimulus was correctly perceived and correctly localized. The independent variables (all within-subject variables) were the *Congruency* (congruent vs. incongruent) between visual and tactile stimuli, and the *Intensity* (sub-threshold vs. supra-threshold) of the tactile stimuli.

In order to investigate the effect of *Congruency* and *Intensity* upon *Response Accuracy*, results were analyzed using a linear mixed-effects model with a logit link function, as implemented in the R package lme4 (Pinheiro & Bates, 2000). Mixed effects models account for the correlations in within-subjects data by estimating subject-specific deviations (or random effects) from each population-level factor (or fixed factor) of interest (see West, Welch, Ga, & Crc, 2007 for an elaboration).

The analysis consisted of 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 (see Appendix, Table 1, illustrating the building of the full model). By default, a random effect was added introducing adjustments to the intercept of the *Subject* variable. In the second step, we searched for the most parsimonious model that fitted the data. To achieve this, the full model was systematically restricted, comparing the goodness of fit using likelihood ratio tests and Akaike's information criterion (Hu, 2007) (see Appendix, Table 2, showing the restricting of the full model). As we were interested in all included variables, fixed effects were never removed from the model. 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; De Ruddere, Goubert, Stevens, Amanda, & Crombez, 2013; Verbruggen, Aron, Stevens, & Chambers, 2010) (see Appendix, Table 3, showing the ANOVA table of the final model).

RESULTS

STAIRCASE

The mean value for the perceptual threshold was significantly different between the left hand (*M* = 0.038W, SD = 0.021), and the right hand (*M* = 0.021W, SD = 0.011, t(29) = 4.02, *p* <0.001). This effect was not different between individuals with right hand dominance (n=25) and individuals with left hand dominance (n=5, t(28) = -1.37, *p* = 0.18), albeit the low number of individuals with left hand dominance may have led to a reduced statistical power.

SELF-REPORT MEASURES

Participants reported to be highly concentrated (*M* = 7.49; SD = 1.35) and to have put much effort to the task (*M* = 8.09; SD = 1.11). Also, participants reported not to be tense/fearful during the task (*M* = 1.49; SD = 1.62). The self-reported attention directed towards the tactile targets was high (*M* = 8.61, SD = 0.87), whereas attention towards the pen was rather low (*M* = 2.78, SD = 1.90). In addition, participants reported not having used the position of the pen to predict the tactile target (*M* = 1.03, SD = 1.48), nor was it experienced as being threatening (*M* = 0.90, SD = 1.27).

RESPONSE ACCURACY TO VIBROTACTILE STIMULI

The model that demonstrated the best fit included only the main effects of the fixed factors, a random subject-based intercept, and a random effect both for *Intensity* and *Congruency*. There was a significant main effect of *Intensity* ($\chi^2(1) = 108.38$, $p < 0.001$, β = −1.57, 95% CI [−1.86 to −1.27]), meaning that *Response Accuracy* was higher for supra-threshold targets trials (*M* = 87.40%; SD = 12.19) compared to sub-threshold targets trials (*M* = 64.38%; SD = 17.18). In addition, there was a significant main effect of *Congruency* ($\chi^2(1) = 17.85$, $p < 0.001$, β = −0.65, 95% CI [−0.96 to −0.35]) revealing that *Response Accuracy* was higher in congruent (*M* = 75.94%; SD = 13.58) trials, compared to incongruent (*M* = 64.32%; SD = 19.75) target trials (Figure 3, top panel).

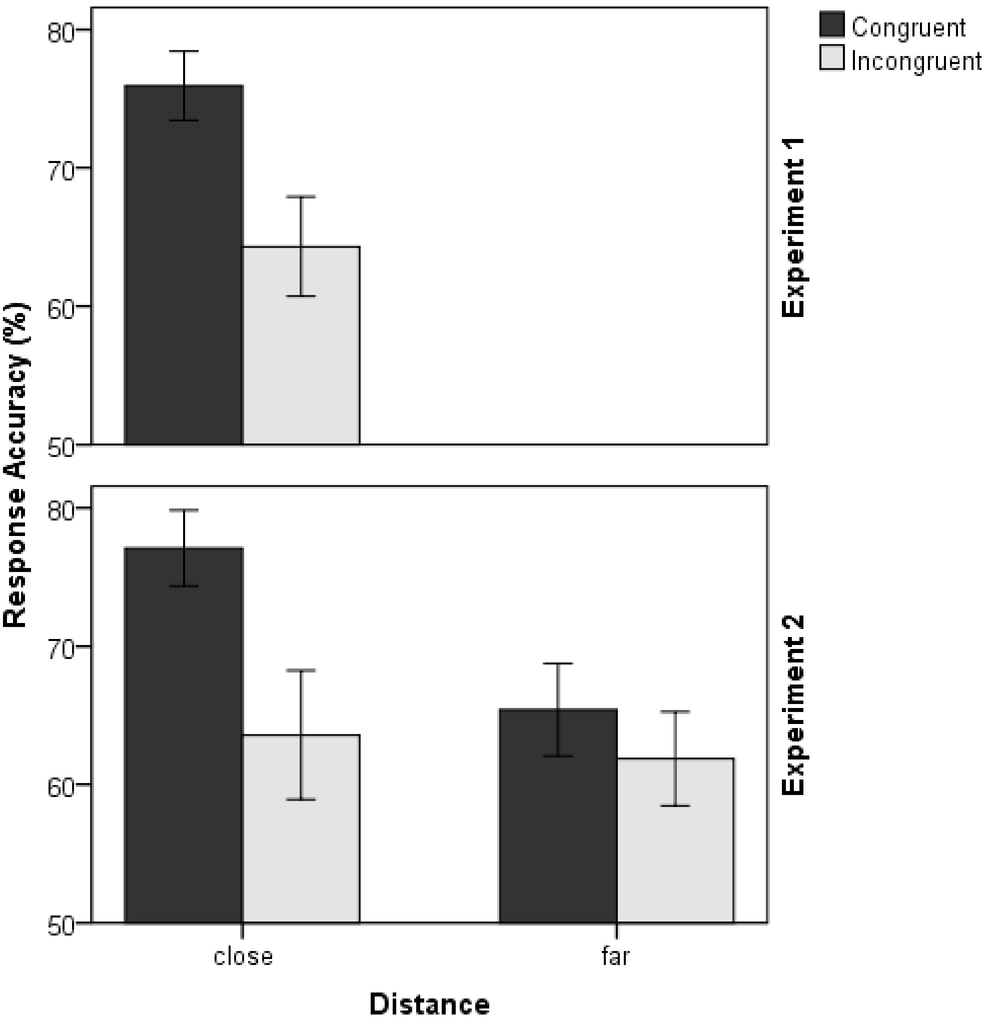

FIGURE 3. Response Accuracy (%) in Experiments 1 and 2, depending on Congruency and Distance of the visual cues. Error bars represent two standard errors of the mean (SEM)

INTERIM DISCUSSION

Experiment 1 shows that *Response Accuracy*, i.e. the ability to perceive and correctly localize the vibrotactile stimuli, was higher when the target location of the approaching visual cue was congruent with the tactile stimulation, as opposed to when it was incongruent. In other words, tactile processing was facilitated at the hand that was approached by the pen. Because in Experiment 1 all visual cues were presented in close proximity to the hands, it was not possible to determine whether the visuo-tactile spatial congruency effect resulted from a crossmodal processing facilitation due to the visual object approaching the proximal location of the stimulated limb, or whether it merely resulted from a response priming effect (i.e. cueing the left vs. right hemi-space primes a response related to that particular hemi-space; see Spence and Driver 1997 for comments on this issue). Therefore, in Experiment 2, the distance of the visual cues towards the hands was manipulated, resulting in an approaching movement close to the participant's hand (i.e. peripersonal space) or far from it (i.e. extrapersonal space).

EXPERIMENT 2

METHOD

PARTICIPANTS

Thirty-five undergraduate students took part for course credits (age: M = 19.66, SD = 4.80, range = 17-44 years; 12 men; 9 left handed). Inclusion and exclusion criteria were the same as in Experiment 1. Due to apparatus failure, data storage was incomplete for 12 participants. As a result, 23 participants (age: M = 19.04, SD = 2.53, range = 17-27 years; 6 men; 7 left handed) were included for further analysis. The study was approved by the Ethics Committee of Ghent University. All participants gave their written informed consent.

STIMULI AND APPARATUS

Stimuli, apparatus, set-up and procedure were similar as in Experiment 1. The main difference was that four – instead of two – metal plates were attached to the table. Two plates were positioned between the thumb and index finger (*close* plates). Two additional plates were placed further away in front of the participants, at 50 cm from the close plates on the same sagittal line (*far* plates) (see Figure 4).

VISUAL AND VIBROTACTILE STIMULI

The same pen was held by the experimenter as a visual stimulus. Now, the pen could approach four different locations defined by respective positions of the two *close* and the two *far*

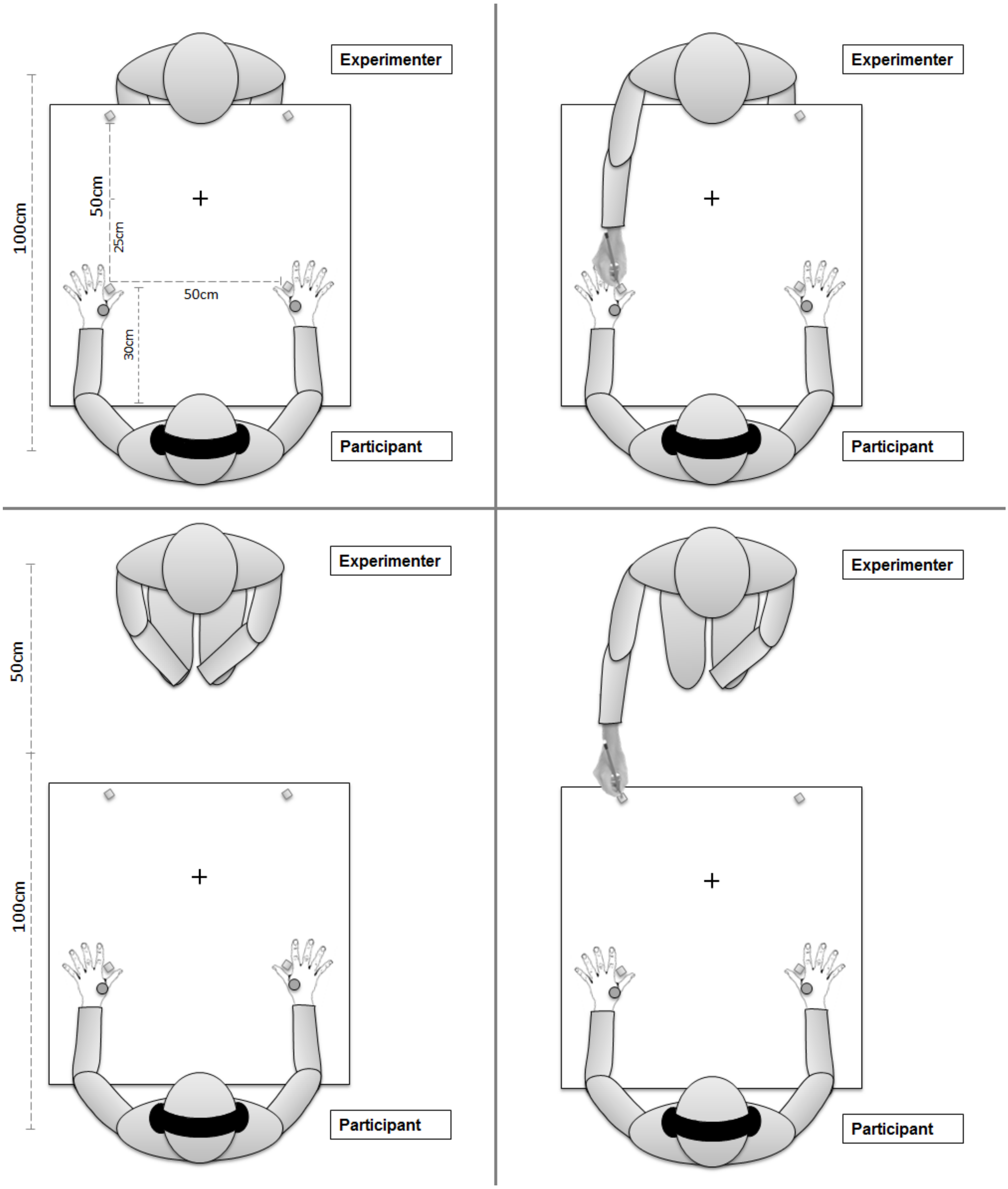

FIGURE 4. Experimental set-up of the IVAO task in Experiment 2. Top panels: *close* condition as seen in Experiment 1. Bottom left panels: *far* condition. The experimenter is seated at a further distance from the participant (left bottom panel), allowing a similar approaching movement as in the *close* condition, but now towards the two *far* contact plates (right bottom panel).

contact plates. The parameters of the vibrotactile stimuli were the same as in Experiment 1, including the staircase procedure to select stimulus intensity.

SELF-REPORT MEASURES.

Questionnaires and self-report measures were identical to those in Experiment 1.

PROCEDURE

The procedure for the self-report measures and the staircase of Experiment 2 were the same as in Experiment 1. The IVAO task was also identical for the stimulation blocks during which the close plates were approached and contacted by the pen. During the other blocks with the far plates, the experimenter was sitting 50 cm further away from the participants in order to maintain the same distance for the approaching movement. The experimenter was also trained to keep about the same speed of movement between the two types of blocks.

The design of Experiment 2 is illustrated in Figure 5. In this experiment, 384 trials, divided into six blocks of 64 trials, were presented. Which plate was to be approached and touched (close vs. far) alternated between blocks. The order of the blocks was randomly assigned. In each block, there were 16 catch trials, 16 congruent unilateral target trials, 16 incongruent unilateral target trials and 16 bilateral target trials (randomly presented). The proportion of 25% of the stimuli at supra-threshold intensity and 75% at sub-threshold intensity was identical as in Experiment 1, resulting in 12 supra-threshold and 36 sub-threshold trials. The number of observations per condition was 12 (4 trials x 3 identical blocks) for supra-threshold targets, and 36 (12 trials x 3 identical blocks) for sub-threshold targets.

ANALYSES

Similar analyses as in Experiment 1 were performed. *Response Accuracy* was analyzed using a linear mixed-effects model with *Congruency* (congruent vs. incongruent), *Cue Distance* (close vs. far) and *Intensity* (low vs. high) as independent within–subjects variables. Follow-up analyses were used when appropriate (see Appendix, Tables 4-6, illustrating the model building procedure).

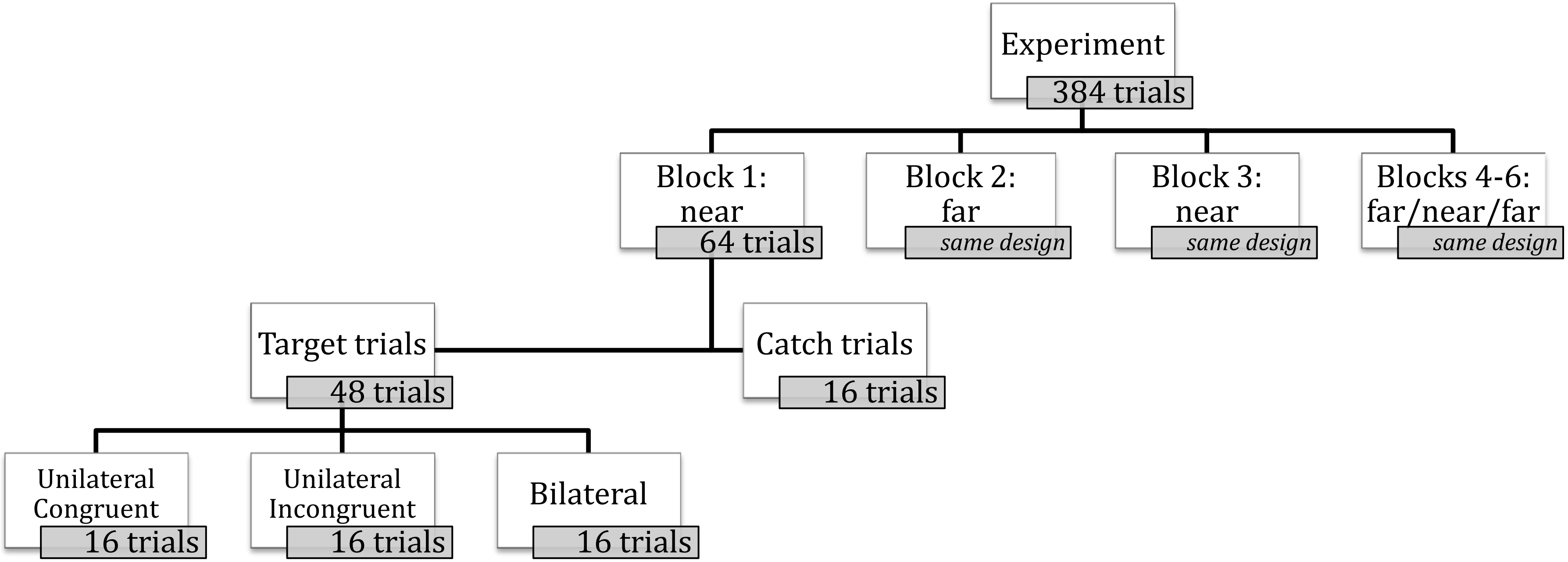

FIGURE 5. Experimental design of Experiment 2. Intensity of the tactile stimuli was above (25%) or below (75%) the perceptual threshold.

RESULTS

STAIRCASE

Perceptual thresholds did not differ between the left and the right hands (left: M = 0.030, SD = 0.022; right: M = 0.035, SD = 0.023; t(22) = -0.66, p = 0.52). Also, there were no differences in perceptual threshold between individuals with right hand dominance (n=16) and individuals with left hand dominance (n=7, t(21) = 1.05, p = 0.31).

SELF-REPORT MEASURES

Results from the self-report measures were similar to Experiment 1. The amount of effort (M = 7.99, SD = 1.34) and concentration (M = 7.61, SD = 1.18) during the task was high. Mean self-reported fear/tension was low (M = 1.49, SD = 1.56). Furthermore, the amount of attention directed towards the tactile stimuli was high (M = 8.44, SD = 1.06), whereas attention towards the pen was quite low (M = 2.99, SD = 1.98). Participants also reported not having used the position of the pen to the predict the location of the tactile stimuli (M = 1.40, SD = 1.45) and felt not threatened by it (M = 0.97, SD = 1.43).

RESPONSE ACCURACY FOR VIBROTACTILE STIMULI

The model that demonstrated the best fit included the main effects of the fixed factors, an interaction between *Congruency* and *Distance*, a random subject-based intercept, and a random effect for *Intensity*, *Congruency* and *Distance*.

We found a significant main effect of *Congruency* ($\chi^2(1) = 27.45$, $p < 0.001$, $\beta = -0.75$, 95% CI [−1.02 to −0.47]), indicating that *Response Accuracy* was higher for congruent trials (M = 71.24%, SD = 13.04) than for incongruent trials (M = 62.73%, SD = 18.27). A significant main effect of *Distance* ($\chi^2(1) = 26.42$, $p < 0.001$, $\beta = -0.66$, 95% CI [−0.91 to −0.41]) indicated a higher *Response Accuracy* when the approaching cue was close to the hands (M = 70.33%, SD = 15.45), compared to when the approaching cue was far from the hands (M = 63.63%, SD = 15.61). *Response Accuracy* was also higher for supra-threshold target trials (M = 84.15%, SD = 14.03) than for sub-threshold target trials (M = 61.26%, SD = 16.41) as shown by a main effect of *Intensity* ($\chi^2(1) = 76.61$, $p < 0.001$, $\beta = -1.47$, 95% CI [−1.80 to −

1.14]). Finally, there was a significant interaction between *Congruency* and *Distance* ($\chi^2 = 16.10$, $p < 0.001$, $\beta = 0.57$, 95% CI [0.29 to 0.85]). Follow-up tests indicate that the difference in *Response Accuracy* between congruent and incongruent trials was significant when cues were presented nearby ($\chi^2(1) = 27.45$, $p < 0.001$), but not when they were presented far ($\chi^2(1) = 1.63$, $p = 0.20$) (Figure 3, bottom panel).

INTERIM DISCUSSION

In Experiment 2, the visuo-tactile congruency effect from Experiment 1 was replicated: *Response Accuracy* was higher when the visual and tactile stimuli were presented on the same location (congruent), compared to the opposite location (incongruent). Moreover, we found that this visuo-tactile spatial interaction was only significant when visual cues were presented near – as opposed to far from the stimulated hands.

GENERAL DISCUSSION

This study investigated whether viewing someone approaching your body alters the perception of a co-occurring tactile stimulus. It was found that the detection accuracy of near-threshold vibrotactile targets on the hands was higher for the visually cued (i.e. approached) hand as compared to the opposite hand (Experiment 1). Moreover, Experiment 2 revealed that this visuo-tactile spatial congruency effect was only present when the pen approached the hand in close proximity (peripersonal space). It was not present when the pen was further away from the hands.

These results are in line with several studies demonstrating the influence of crossmodal interaction on the processing of somatosensory stimuli (Làdavas & Farnè, 2004; Spence et al., 1998). However, in most of those studies static – as opposed to dynamic - visual stimuli have been used, reducing the generalizability to real-life (clinical) situations. Yet, since an important function lies within localizing stimuli events surrounding the body, it seems reasonable that stimuli *approaching* the body require full attentional processing. Therefore, this study has investigated and confirmed the enhancing effect of approaching (i.e. dynamic) visual stimuli on tactile sensitivity. The latter might especially be important for health care providers, performing somatosensory examinations on patients by approaching them with a measuring device or with their hands. For example, during the examination of neuropathic pain, Quantitative Sensory Testing (QST) is a well-used diagnostic tool that requires approaching a patient while measuring sensory symptoms. Also, when doctors verify the diagnosis of complex regional pain syndrome, they need to assess a series of (sensory) symptoms (e.g. hyperesthesia) by approaching and touching the affected hand (e.g. with a von Frey filament or algometer) (Harden, 2010; Harden et al., 2010). In these cases, approaching the patient might lead to a momentary increased sensitivity for touch, and thereby to an overestimation of the evaluated symptom. Based on this study, it is not yet possible to determine the magnitude of this increased sensitivity nor to conclude that it could effectively lead to misdiagnosis. However, it may be useful for clinicians to be aware of this phenomenon and to take it into account when conducting somatosensory evaluations on patients. For example, doctors could choose to instruct patients to close their eyes while being examined, to prevent visual feedback (Keizer, van Wijhe, Post, & Wierda, 2007).

During the last decades, researchers have gained interest in the interaction between visual and somatosensory information *near the body*. Several authors have proposed that when encountering a stimulus event surrounding the body, combining information from the different senses (i.e. crossmodal interactions) might provide the best estimate of the external event (Driver & Spence, 1998a, 1998b; Làdavas & Farnè, 2004). Researchers have conducted extensive behavioral, as well as electrophysiological and brain imaging research to support this notion (Calvert et al., 1999, 2000; Driver & Spence, 1998a; Macaluso & Driver, 2001; Sathian et al., 1997). There it was also found that these crossmodal influences mainly take place near the body (Làdavas, di Pellegrino, Farnè, & Zeloni, 1998; Làdavas, 2004), in the so-called peripersonal space (Rizzolatti, Fadiga, Fogassi, & Gallese, 1997). Kandula, Hofman and Dijkerman (2015) explain that information coming from peripersonal space can be of higher significance in terms of processing as: *i)* this region is the only space surrounding the body in which stimuli can be interacted with; *ii)* stimuli in this region (close to the body) could be potentially more harmful for the body's integrity. Our results corroborate these findings. Which neural/psychological mechanisms underlie these findings is still subject of investigation. There are at least three possible explanations (see review in Spence & Driver, 2004).

First, our findings may be explained by *spatial attention*, meaning that the perception of a stimulus in one modality will attract attention towards its location, increasing the chance of nearby stimuli from other modalities being detected (Spence & Driver, 2004). Apart from this rather *bottom-up* approach to spatial attention, a *top-down* anticipatory component might also increase attention towards the approached body part. A recent study (Kandula et al., 2015) has suggested that a prediction mechanism underlies the effect of approaching visual stimuli on temporal/spatial tactile judgments. Accordingly, participants in our study could have been hard-wired to anticipate the occurrence of a tactile stimulus on their approached hand, even if this was only the case in a minority of the trials (25% congruent unilateral target trials and 25% bilateral target trials). This *top-down* anticipation may then have evoked heightened *spatial attention* to the location of the approached body part, resulting in higher detection accuracy.

Second, stimulus-driven *'multisensory integration'* may as well lay at the foundation of crossmodal interaction effects. This implies that information from different sensory modalities is processed in unity, as if it were originating from a common source of input, provided that these multiple sources of input correspond in both time and space (Spence & Driver, 2004).

A third and related explanation originates from animal studies demonstrating visuo-tactile integration near the body at the single-neuron level (Duhamel, Colby, & Goldberg, 1998; Graziano & Gross, 1995, 1998; Rizzolatti, Luppino, & Matelli, 1998; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981). Neurons in brain areas such as the ventral premotor area and the ventral intraparietal sulcus have been shown to process inputs from different sensory modalities (Duhamel et al., 1998; Graziano & Gross, 1995, 1998; Graziano, Hu, & Gross, 1997). More specifically, neurons in this region are found to have multimodal receptive fields (RFs), meaning that they respond to stimuli from different modalities who are present within a common region of space on and/or around the body. Graziano et al. (1997), for example, have demonstrated that bimodal neurons from the ventral premotor cortex in monkeys fire for both tactile and visual stimuli when visual stimuli are in proximity to the tactile RF. Especially visual stimuli approaching the body were found to be targeted by these bimodal neurons (Graziano & Gross, 1995; Graziano et al., 1997). One of the key features of these neurons is that their visual RF is spatially locked to the tactile RFs, meaning that they move in space with the body part the code, independently of the position of the triggering visual stimuli on the retina. This functional property of bimodal neurons might explain why participants in our study were better in detecting tactile targets who were accompanied by a visual cue in the peri-hand space (*congruent-close* unilateral target trials) as compared to the contralateral hemi-space (*incongruent-close* unilateral target trials) and the extrapersonal space (*far* unilateral target trials). Additional research is needed to determine which of these underlying mechanisms is responsible for the increased tactile sensitivity after visual approach.

There are some limitations to this study. First, the approaching movement was not mechanically standardized. Therefore, the exact duration and trajectory of the stimulus could have slightly differed between trials. Second, the use of an ecologically valid stimulus such as an approaching hand has some disadvantages. Although our studies show that approaching someone with real hands has particular effects, we have less control over potentially confounding effects, such as, for example, the increasing size of an approaching object on the retina. However, despite the fact the retinal size of visual stimuli are usually controlled in experimental settings, this effect is unlikely to have played a major role in our date since it was shown there is no strict scaling relationship between retinal image size and the importance of its perception. For instance Murray et al. (2006) have shown that the V1 cortical responses to visual stimuli do not merely depend of their retinal sizes but already integrate other contractual information such as the perception of deepness. Third, there was a lack of orthogonality between the direction of the visual cue (left vs. right) and the direction of the responses (also left vs. right). Non-orthogonal response mapping can lead to the misconception that actual crossmodal interactions are at work, whereas it might only be hemispheric activation, priming a congruent response (Spence & Driver, 2004). However, the lack of crossmodal interactions in extrapersonal space in Experiment 2 proves that response priming cannot have (fully) explained the current results. Fourth, the detection and localization of tactile stimuli was measured as outcome variable, but not its rated intensity, impeding us to draw any conclusions on the size of changes in tactile sensitivity. Related to that, participants in our study did not experience pain nor did they undergo painful target stimuli, although this might often be the case in clinical examinations. The IVAO paradigm may be easily adapted to address these pertinent questions. Future research should especially meet the need for multisensory research in the context of pain. Despite the high current popularity of this topic, clear evidence is still lacking (Torta, Legrain, & Mouraux, 2015; Valentini, Kock, & Aglioti, 2015).

In conclusion, the current study provides evidence on the effect of nearby approaching movements on tactile detection accuracy. We developed the In Vivo Approaching Object paradigm as a straightforward and ecologically valid method to measure visuo-tactile interactions around the body. Our findings suggest that changes in tactile sensitivity due to approaching movements might not only occur in research settings, but also in medical settings.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest related to the present study.

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APPENDIX

Model	Test	Random	AIC	Df	χ²	*p*-value
1	Initial fit	1	4087.8	5		
2	Random Congruency (1 vs. 2)	1 + Congruency	4041.8	7	χ²(2) = 50.00	<0.001
3	Random Congruency and Intensity (2 vs. 3)	1 + Congruency + Intensity	4038.8	10	χ²(3) = 8.94	0.03

TABLE 1. Step 1 Experiment 1. Determine random effects structure, all models have 'subject' as random intercept. Decision: random effect for Congruency and Intensity added: keep model 3.

Model	Test	Fixed	AIC	Df	χ²	*p*-value
1	Initial fit	Congruency * Intensity	4038.8	10		
2	Remove interaction (1 vs. 2)	Congruency + Intensity	4037.4	9	χ²(1) = 0.57	0.45

TABLE 2. Step 2 Experiment 1. Determine fixed effects – Trim down the model. Decision: choose model 2 without the interaction between Congruency and Intensity.

Effects	***B***	**SE(B)**	χ²	Df	*p*
Intercept	2.60	0.19	193.02	1	<0.001
Congruency	-0.65	0.15	17.85	1	<0.001
Intensity	-1.57	0.15	108.38	1	<0.001

TABLE 3. Step 3 Experiment 1. Test final model.

Model	Test	Random	AIC	Df	χ^2	*p*-value
1	Initial fit	1	5067.5	9		
2	Random Congruency (1 vs. 2)	1 + Congruency	5049.2	11	$\chi^2(2)$ = 22.28	<0.001
3	Random Congruency and Intensity (2 vs. 3)	1 + Congruency + Intensity	5037.5	14	$\chi^2(3)$ = 17.71	<0.001
4	Random Congruency, Intensity and Distance (3 vs. 4)	1 + Congruency + Intensity + Distance	5028.2	18	$\chi^2(4)$ = 17.22	0.002

TABLE 4. Step 1 Experiment 2. Determine random effects structure, all models have 'subject' as random intercept. Decision: random effect for Congruency, Distance and Intensity added: keep model 4.

Model	Test	Fixed	AIC	Df	χ^2	*p*-value
1	Initial fit	Congruency * Intensity * Distance	5028.2	18		
2	Only two-way interactions (1 vs. 2)	Congruency*Intensity + Congruency*Distance + Intensity*Distance	5026.4	17	$\chi^2(1)$ = 0.11	0.74
3	Without interaction with Intensity (2 vs. 3)	Congruency*Distance + Intensity	5023.8	15	$\chi^2(2)$ = 1.43	0.49
4	Without interaction with Distance (2 vs. 4)	Congruency*Intensity + Distance	5036.8	15	$\chi^2(2)$ = 14.48	<0.001
5	Without interaction with Congruency (2 vs. 5)	Distance*Intensity + Congruency	5035.7	15	$\chi^2(2)$ = 13.31	<0.001
6	Without interactions (3 vs. 6)	Congruency + Distance + Intensity	5035.2	14	$\chi^2(1)$ = 13.37	<0.001

TABLE 5. Step 2 Experiment 2. Determine fixed effects – Trim down the model. Decision: choose model 3 with the interaction between Congruency and Distance.

Effects	***B***	**SE(B)**	χ^2	Df	*p*
Intercept	2.57	0.20	157.46	1	<0.001
Congruency	-0.70	0.14	25.13	1	<0.001
Distance	-0.61	0.13	23.36	1	<0.001
Intensity	-1.45	0.16	83.81	1	<0.001
Congruency*Distance	0.52	0.14	13.58	1	<0.001

TABLE 6. Step 3 Experiment 2. Test final model.

CHAPTER 3

SEEING “YOUR” RUBBER HANDS BEING TOUCHED INCREASES TACTILE SENSITIVITY[3]

ABSTRACT:

When something touches the body, the brain calculates its position with respect to the body by integrating information from different sensory modalities. Although it is known that both visual and proprioceptive information are important in mapping the position of stimuli on the body, their unique contributions to spatial perception remain difficult to disentangle. The aim of this study was to investigate the role of visual information, irrespective of proprioception, in the localization of somatosensory stimuli on the body. Therefore, we tested whether tactile processing is enhanced when a person views a neutral object approaching the body (= visual information), even when it approaches a fake body-part (i.e. independent from proprioception). In a rubber hand illusion study, participants (N = 52) detected and localized near-threshold vibrotactile stimuli on the left, the right or on both hands, hidden from sight. This was shortly preceded by the experimenter making an approaching movement towards a target point above the participant’s left or right hand, either on the same or the opposite side of the (unilateral) tactile targets. In half of the trials, the experimenter approached rubber hands that were positioned above the participant’s real hands to create the visual illusion of the rubber hands being the real hands. Tactile detection accuracy (TDA) was calculated and expected to be higher when the tactile target was on the approached side, especially when rubber hands were approached and when participants perceived the rubber hand as their own. In line with our hypotheses, TDA was higher for tactile targets on the approached side. This visuo-tactile congruency effect was even stronger when rubber hands were present. Self-reported embodiment with the rubber hands did not have a clear effect. In conclusion, we found a crossmodal effect of seeing someone approaching your body on tactile sensitivity, that was more pronounced when the approached body-parts were visible than when they were invisible. These results suggest that knowledge about the location of body-parts (i.e. proprioception) might be sufficient to elicit crossmodal effects, but that, in addition to that, vision of the approached body-parts further enhances these crossmodal effects.

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[3] Van der Biest, L., Legrain, V., De Paepe, A.L., Crombez, G. (unpublished manuscript). Seeing “your” rubber hands being touched increases tactile sensitivity.

INTRODUCTION

When moving through the world, we experience a clear separation between our body and the space surrounding it. However, we often encounter objects or persons that interrupt this separation by touching our body. When we detect something from the environment (nearly) touching our body, the brain localizes the source of the somatosensory stimulation to prepare adequate responses (Haggard, Taylor-Clarke, & Kennett, 2003). Several modes of representation are possible in coding the location of somatosensory stimuli. At a primary level, a somatotopic representation of the skin is used to code the position of somatosensory stimuli on the body in a specific sub-group of neurons in the cortical brain (Narici et al., 1991; Penfield & Boldrey, 1937; Penfield & Rasmussen, 1950). However, as the positions of the body parts are relative to each other, the sole use of somatotopic representation might on some occasions be inappropriate to identify the position of that object in contact with the body. For example, when being touched on the left hand while crossing the arms, i.e. when the left hand lies in the right part of space, the brain is still able to understand that the contact on the left hand is coming from an object in the right side of space (Macaluso & Maravita, 2010). In such situations, spatiotopic representations of the body may be used to remap the location of somatosensory stimuli according to external coordinates by integrating proprioceptive inputs (Azañón, Longo, Soto-Faraco, & Haggard, 2010; Macaluso & Maravita, 2010; Rizzolatti, Fadiga, Fogassi, & Gallese, 1997; Spence, Pavani, & Driver, 2000). In addition, to adapt the behavior to the object in contact with the body, it is also of importance to coordinate the perception of its impact on the body space with the perception of its location in external space. Integrating visuospatial coordinates allows the brain extending the representations of the body in external proximal space (Graziano & Gross, 1995; Macaluso & Maravita, 2010).

Evidence for such spatiotopic representations comes from crossmodal spatial attention studies stating that the combination of multisensory inputs generates a more accurate and coherent perception of our surroundings (Spence & Driver, 2004; Spence, 2010). Various studies using spatial cueing paradigms have revealed the effect of visual stimuli on tactile perception (Driver & Spence, 1998; Eimer, 2001; Macaluso & Driver, 2001; Spence, Nicholls, Gillespie, & Driver, 1998). When attention is voluntarily focused toward or captured by a visual stimulus in a specific part of space, the processing of a tactile stimulus is facilitated, but only under certain conditions: *i)* the hand on which the tactile stimulus is applied should be placed close to the visual stimulus and *ii)* the visual stimuli should, depending on the underlying mechanism, briefly precede the tactile stimuli, or at least occur in the same time window (Eimer & Driver, 2001; Kennett, Eimer, Spence, & Driver, 2001; Spence & Driver, 1996; Spence et al., 1998).

Although the effect of visual stimuli near the body on tactile perception is well-established, it is unclear whether the perception of this spatial proximity is driven by vision (e.g. *seeing* your body-parts relative to that visual stimulus, or rather by proprioception (e.g. *feeling* your body-parts on that location). In some studies, this question has been addressed by occluding participants' vision of their body-parts. For example, Kennett, Spence and Driver (2002) found that even when participants' hands were hidden, their ability to discriminate tactile stimuli applied to either the thumb or the index finger was better when the tactile stimuli were preceded by a visual stimulus applied near the stimulated hand, compared to when the visual stimulus occurred near the opposite hand, whatever the relative position of the hands in external space. Despite the relevance of proprioceptive information proposed by these types of studies, evidence is also available suggesting a role for vision. For example, Gallace and Spence (2005) found that performance on temporal order judgments of tactile stimuli on the hands, previously shown to be worsened by decreasing the distance between the hands (Shore, Gray, Spry, & Spence, 2005), was influenced by the *visually perceived* distance between the hands, although the actual distance was held constant. Pavani et al. (2000) observed that reaction times to tactile stimuli were affected by the occurrence of visual stimuli near the stimulated hand. Crucially, the effect of the visual stimuli on tactile reaction times was also observed when the visual stimuli were delivered close to a fake rubber hand that was aligned realistically with the real hand that was hidden from sight. Wesslein, Spence, and Frings (2014) also found an enhancing effect of viewing rubber hands on tactile processing on the unseen real hands, provided participants experienced the rubber hands as belonging to their body. This sense of embodiment has been put forward as a pathway, explaining the effect of viewing a stimulated body-part – real, fake, or elongated by tool-use – on tactile processing (Farnè, Iriki,

& Làdavas, 2005; Igarashi, Kimura, Spence, & Ichihara, 2008; Igarashi, Kitagawa, & Ichihara, 2004; Igarashi, Kitagawa, Spence, & Ichihara, 2007). More specifically, it has been argued that the influence vision exerts over touch is modulated by the activation of a body schema that presets the unisensory somatosensory cortex (Haggard, Christakou, & Serino, 2007; Wesslein et al., 2014).

Unlike many of the experimental situations discussed in the previous paragraphs, in real life the body and stimuli in its surroundings are often in motion relatively to each other. Mimicking real life situations may then require dynamic – as opposed to static – visual stimuli in crossmodal attention studies. Yet, few authors have adopted dynamic visual stimuli to investigate visuo-tactile interactions near the body in humans. A couple of studies (e.g. Canzoneri, Magosso, & Serino, 2012; De Paepe, Crombez, & Legrain, 2016; Graziano, Yap, & Gross, 1994; Makin, Holmes, Brozzoli, Rossetti, & Farnè, 2009; Van der Biest, Legrain, De Paepe, & Crombez, 2016) did acknowledge the relevance of approaching visual stimuli on tactile perception in humans. Nevertheless, none of those have fully disentangled the relation between vision and proprioception in the context of somatosensory perception.

In the current study, we used dynamic stimuli to investigate the effect of visual cues on tactile sensitivity. In addition, we wanted to disentangle the respective roles of visual information vs. proprioceptive information. We therefore occluded participants' vision of their hands and placed fake rubber hands realistically in front of them to elicit the illusion that the fake hands were in fact theirs. Once the illusion is created, stimuli near the fake hands tend to elicit similar behavioral and neural responses than stimuli near the real hands (Armel & Ramachandran, 2003; Ehrsson, 2007), but without proprioceptive feedback from the real hands. As such, we dissociated between the illusory visual location and the perceived proprioceptive/somatotopic location of the hands to investigate *i)* whether approaching participants' *unseen* hands increases tactile sensitivity of the approached hand; *ii)* whether viewing a realistically aligned fake hand being touched further improves tactile sensitivity; *iii)* and whether the effect of approaching fake hands is dependent on a sense of embodiment with the fake hands.

In each trial, the experimenter approached a target point above one of the participants' occluded hands, either in the left or the right hemi-field. This was followed by a near-threshold (sub- or supra-threshold) tactile stimulus on the hand in the same hemi-field (congruent trials) or in the other hemi-field (incongruent trials). In half of the trials, rubber hands were positioned in front of the participants and were approached instead. Tactile detection accuracy (TDA) was compared between congruent and incongruent trials and between trials with and without rubber hands. We expected *i)* that TDA would be higher for congruent trials (compared to incongruent trials); *ii)* that this visuo-tactile congruency effect would be larger when the rubber hands were present (compared to absent); and *iii)* that this effect of the rubber hands on visuo-tactile congruency would be modulated by the level of experienced embodiment.

METHOD

PARTICIPANTS

Fifty-five undergraduate students (age: *M* = 22.67, SD = 4.31, 13 men, 7 left handed) took part in this study and were compensated €10 after completion of the experiment. Participants were excluded when they reported insufficiently corrected visual impairments, current medical/psychiatric conditions or medication intake affecting somatosensory sensitivity. None of the participants had to be excluded for these reasons. However, due to software failure, data storage was incomplete for three participants. Fifty-two participants were included for further analysis (age: *M* = 22.54, SD = 4.34, 13 men, 7 left handed). The study was approved by the Ghent University Ethics Committee and all participants gave their written informed consent.

STIMULI AND APPARATUS

Participants were seated with their hands, palms down, lying on a table (Figure 1, panel A). Visibility of the participant's hands was prevented by an aluminum board (70 x 50cm width x 10cm height) placed on top of the table and above the participant's hands. A black sheet was also draped around the participant's trunk and arms and attached to the metal board to occlude vision of the upper limbs. At a distance of 40cm from the edge of the table, a fixation cross was present in front of the participant, preventing gaze shifts. A chin wrest additionally fixated the participant's head. Each participant wore headphones through which white noise (46dB) was presented to mask auditory stimuli from the immediate environment. The experimenter sat on the opposite side of the table, facing the participant (~1m distance between experimenter and participant).

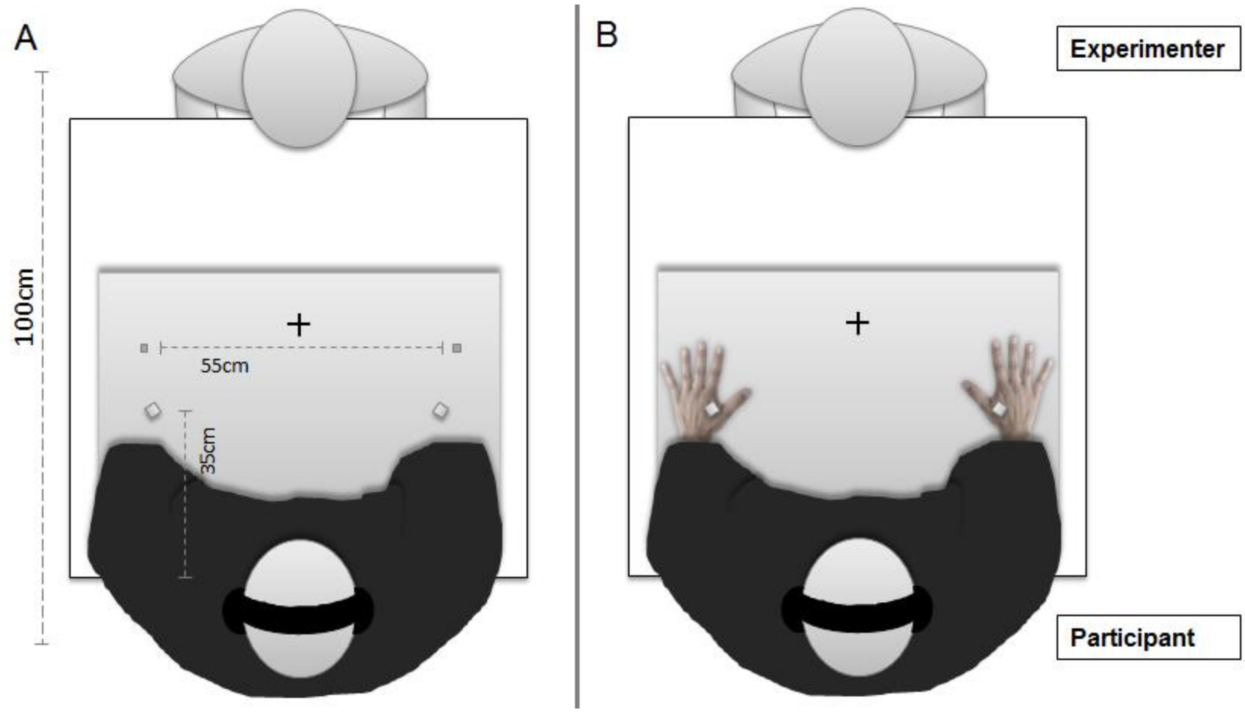

FIGURE 1. Experimental set-up of the IVAO task. Participants were seated across the experimenter with their hands, hidden from sight, under a metal board. Rubber hands were either absent (Panel A) or present (Panel B) on top of the metal board to elicit the illusion that the rubber hands were the real hands. A black sheet was draped around the trunk to occlude participants' vision of their upper body and extremities.

RUBBER HANDS

In one condition, two rubber hands (one left and one right prosthetic rubber glove; Vigo, Wetteren, Belgium) were placed *on top of* the metal board, directly above the real hands lying *underneath* the board (Figure 1, panel B). The rubber hands were placed in such a manner that they spatially corresponded to the position of the real hands. As a result, the rubber hands visually appeared to be as the real hands. In order to ensure the actual spatial correspondence between the real and the rubber hands, spatial reference points were used (Figure 2). Participants' middle finger tips rested on a square foam ($1cm^2$), attached to the table at a distance of 35cm from the edge of the table and 55cm apart. Two identical foams were attached on top of the metal board, exactly above the lower foams, and supported the rubber hands' fingertips. In the other condition, no rubber hands were presented in front of to the participants (Figure 1, panel A).

FIGURE 2. Illustration of the position of the hands (real and fake). Participants' middle fingertips rested on foam cubes (indicated by arrows), used as spatial reference points to ensure the spatial correspondence between the real and the fake hands.

VISUAL STIMULI

A black pen-like object, held by the experimenter (LVDB, female), was used to approach the participant on the left or right side (Figure 3, panels A and B). Serving as electrical contacts for the pen, two square metal plates (4cm^2 large and 50cm apart) were attached on top of the metal board at a distance of 25cm from the edge of the metal board and table. In addition, two identical plates were present on the rubber hands, between thumb and index finger. In trials where the rubber hands were absent, the experimenter approached and tapped the contact plates on the board, whereas when rubber hands were present, the plates on the rubber hands were approached and tapped instead. In both cases, tapping one of these contact plates enabled the occurrence of a tactile stimulus.

VIBROTACTILE STIMULI

Exactly underneath these contact plates, a magnet linear actuator (C-2 TACTOR, Engineering Acoustics Inc., Casselberry, Florida) was attached to the sensory territory of the superficial radial nerve of each hand and released vibrotactile stimuli (50ms duration, 50Hz). The actuators were driven by self-developed software and controlling devices that converted electrical signals into oscillating movements of the actuators against the skin. The intensities of the vibrotactile stimuli were near the perceptual threshold, which was individually determined using a staircase procedure. The staircase comprised four separate but intermixed series of 20 trials (two series for each hand) that were randomly administered (80 trials in total). The starting value of each series was 0.068W for the first stimulus. The intensity decreased each time the participants reported feeling the stimulus, and increased when no sensation was reported. The perceptual threshold was determined for each hand, based upon the mean intensity of the last stimulus of each of the two series of that particular hand. *Sub-threshold* and *supra-threshold* values were calculated for each hand by respectively subtracting one eighth from the perceptual threshold value, or adding one eighth to it (see Press, Taylor-Clarke, Kennett, & Haggard, 2004).

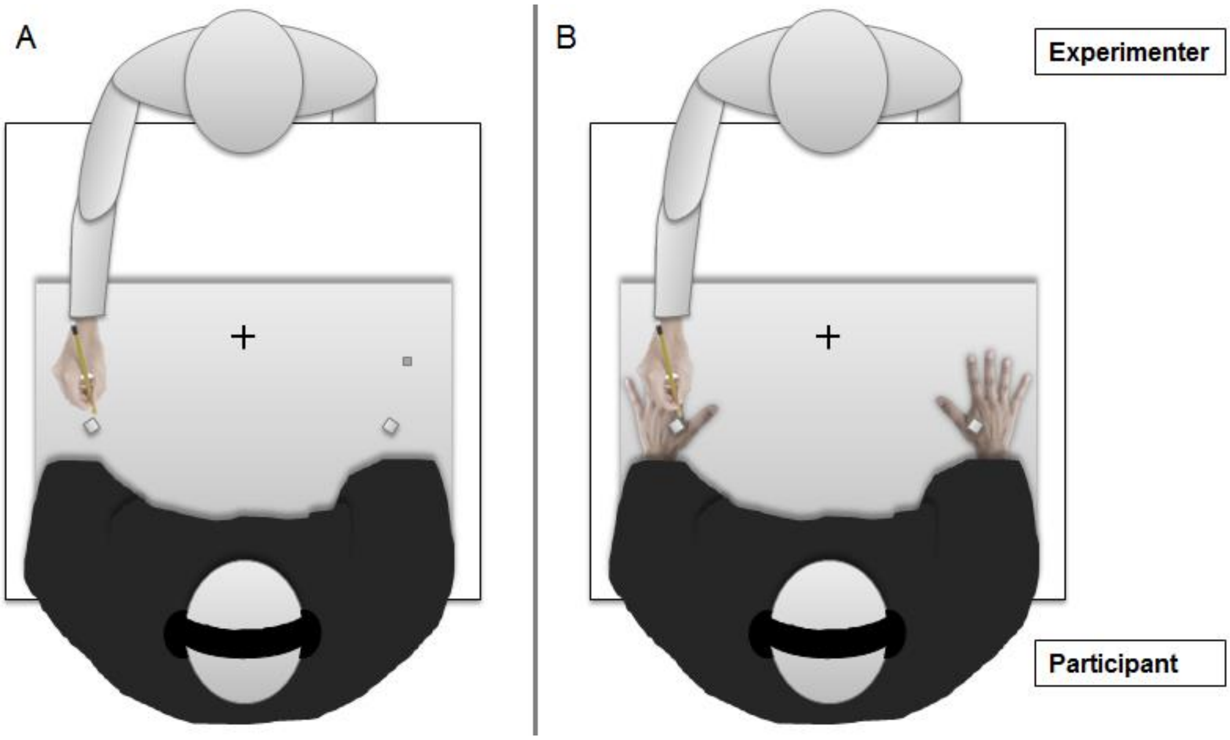

FIGURE 3. Illustration of the experimental conditions. During each trial, the experimenter approached one of the contact plates (left vs. right) directly above the participant's hands with a pen (Panel A). In the condition were rubber hands were present (Panel B), one of the contact plates on the rubber hands (also directly above the participant's hands) were approached.

SELF-REPORT MEASURES

Participants completed an anamnestic questionnaire comprising items on socio-demographics, current treatments and/or medication intake for medical or psychiatric conditions, and perceived health quality. The Pain Grading Scale (PGS; Von Korff, Ormel, Keefe, & Dworkin, 1992) was also included in the questionnaire to assess pain and disability during the last six months. Participants also filled in the Dutch versions of the Patient Health Questionnaire (PHQ-15; Kroenke, Spitzer, & Williams, 2002), the Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995) and the Trait Scale of the State-Trait Anxiety Inventory (STAI; Spielberger, 1987). The PHQ-15, PCS and STAI were used for meta-analytic purposes and will therefore not be further discussed. At the end of each block, a series of self-report items was completed by the participants, measuring the amount of effort and concentration and fear/tension during the task, the amount of attention directed to the visual and tactile stimuli presented during the task, the extent to which the pen was perceived as threatening and to which it was consciously used to predict the position of the tactile targets. Each item was rated on an 11-point graphic rating scale, ranging from 0 ("not at all") to 10 ("very much").

In addition, a short Rubber Hand Illusion (RHI) survey, consisting of 9 items, was completed that measured to what extent participants experienced the illusion of perceiving the rubber hands as belonging to their own body. Items were based on the original survey of Botvinick and Cohen (1998) and on additional items of Pavani, Spence and Driver (2000) and Wesslein, Spence and Frings (2014), which were further adapted to fit our study design. Participants reported to what extent *i)* it seemed as if they felt the touches on their hands where they saw the rubber hands being touched; *ii)* it felt as if the rubber hands were their own hands; *iii)* it felt as if their real hands drifted upwards (towards the rubber hands); *iv)* it seemed as if they had more than one hand or arm; *v)* it seemed as if the touches they felt originated from somewhere between their own hands and the rubber hands; *vi)* it felt as if their real hands became 'rubbery'; *vii)* it felt as if the black pen came close to their real hands; *viii)* they felt that they saw their own hands lying on the board; *ix)* they felt that the rubber hands belonged to their own body. Each item was presented for both the left and the right hand and was measured on a 7-point graphic rating scale ranging from -3 ("I strongly disagree") to 3 ("I strongly agree").

PROCEDURE

Participants started by filling out the general questionnaire, the PHQ-15, the PCS and the STAI. This was followed by the staircase procedure during which participants were instructed to lay their arms on the table with the tips of their middle fingers resting on the foam squares. The height of the chin wrest was adjusted to ascertain a comfortable position. After having given instructions about the staircase, headphones were positioned and turned on. In the middle of a computer screen, placed in front of the participant at a distance of approximately 50cm, a visual stimulus (a letter X, 1000ms duration) appeared and signaled the immediate occurrence of a low intensity tactile stimulus on the left or right hand (laterality unknown to participant). The participant reported on each occasion whether the tactile stimulus was perceived ("yes" or "no"). Responses were inserted manually by the experimenter on a keyboard. After completion of the staircase procedure, the headphones and the computer screen were removed.

During the *In Vivo Approaching Object* (IVAO) task, participants were instructed to fixate on the fixation cross and to lay their hands on the table, fingertips resting on the foams. The experimenter initiated each trial by approaching the participant's left or right side with a pen (visual cue). In the no-RH condition, no rubber hands (RH) were present and the left or right contact plate on the board was approached and tapped. In the RH condition, two rubber hands were positioned realistically on the metal board, and the metal plates on the rubber hands were tapped instead.

The experimenter (LV, female) was trained to perform the approaching and retracting movement in a standardized manner (~1s approach and ~1s retract). The visual cue co-occurred with a sub-threshold or supra-threshold vibrotactile stimulus on the hands in 75% of the trials (target trials). In the remaining 25% of the trials, no tactile target was provided (catch trials). The tactile stimulus could be present on the same side as the visual cue (congruent unilateral target trials), on the other side (incongruent unilateral target trials) or on both sides (bilateral target trials). The participants verbally responded upon the sensation of the tactile target on the hands: "no sensation", "left sensation", "right sensation" or "both sides sensation" (manually inserted by the experimenter on a keyboard: 0, 4, 6, 5 keys respectively). Instructions about which side to approach were visible for the experimenter on a computer screen but were hidden from the participant's view. Nevertheless, the experimenter was blind as to which type of trial (congruent/incongruent/bilateral/catch) was running. The experimental design is illustrated in Figure 4. A total of 384 trials was delivered across six experimental blocks. The first and last three blocks differed in the presence of the RHs (RH-RH-RH/noRH-noRH-noRH or noRH-noRH-noRH/RH-RH-RH, presented randomly). Each block consisted of four types of trials, each distributed randomly: 16 congruent, 16 incongruent, and 16 bilateral target trials and 16 catch trials. In 75% of the target trials, a sub-threshold target was presented, as opposed to a supra-threshold target in the remaining 25% of those trials. Supra-threshold trials were presented to allow the participants a sense of mastery over the task. The number of

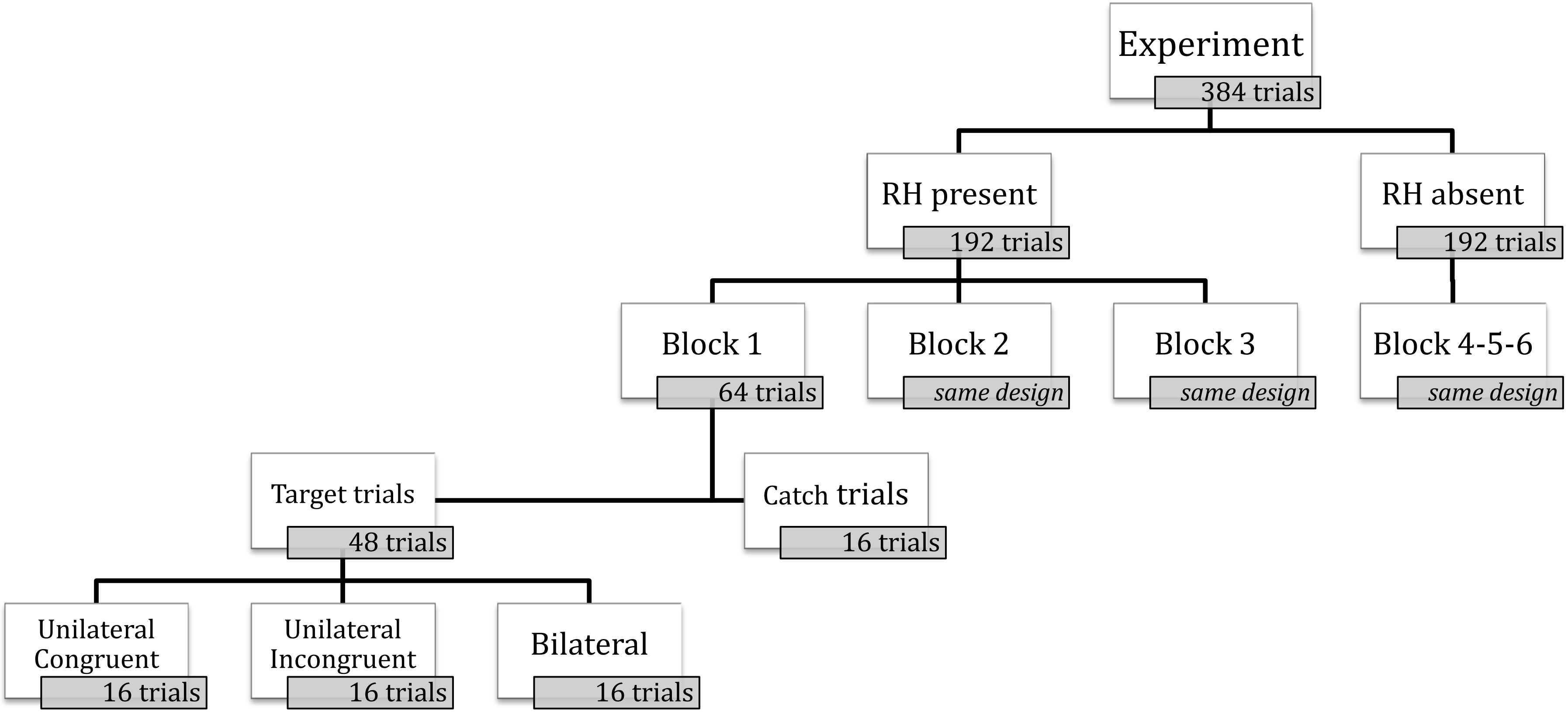

FIGURE 4. Experimental design of IVAO study. Intensity of tactile stimuli was below (75%) or above (25%) the perceptual threshold.

observations per condition was 36 (12 trials x 3 identical blocks) for sub-threshold targets and 12 (4 trials x 3 identical blocks) for supra-threshold targets.

ANALYSIS

The outcome variable of the analysis was *Tactile Detection Accuracy (TDA)*, defined as a binomial variable (correct vs. incorrect). A response was considered as correct when a participant correctly detected and localized a tactile target during a trial. Only unilateral target trials were included in the analysis; bilateral and catch trials were discarded. Independent variables (all within-subject variables) were the *Congruency* (congruent vs. incongruent) between visual cues and tactile targets, the *Presence* (present vs. absent) of the rubber hands and the *Intensity* (sub-threshold vs. supra-threshold) of the tactile targets.

A linear mixed-effects model with a logit link function, as implemented in the R package lme4 (Pinheiro & Bates, 2000) was used to analyze the effect of *Congruency, Presence* and *Intensity* on *TDA*. The analysis consisted of three steps. First, all relevant factors and interactions were entered in the model as fixed factors, and a random effect was added 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 (see Appendix, Tables 1 and 4). By default, a random effect was added allowing adjustments to the intercept of the *Subject* variable. In the second step, we trimmed the model to find the most parsimonious model. To achieve this, the full model was systematically restricted, comparing the goodness of fit using likelihood ratio tests and Akaike's information criterion (Hu, 2007) (see Appendix, Tables 2 and 5). As we were interested in all included variables, fixed effects were never removed from the model. 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; De Ruddere, Goubert, Stevens, Amanda, & Crombez, 2013; Verbruggen, Aron, Stevens, & Chambers, 2010) (see Appendix, Tables 3 and 6).

RESULTS

STAIRCASE

Perceptual thresholds did not differ between left and right hands (left: M = 0.0305, SD = 0.0216; right: M = 0.0260, SD = 0.0220; t(51) = 1.22, p = 0.23).

SELF-REPORT MEASURES

Overall, participants reported a high level of effort (M = 7.93, SD = 1.86) and concentration (M = 7.86, SD = 1.21) dedicated to the task. Fear or tension during the task was low (M = 1.13, SD = 1.70). The self-reported amount of attention directed towards the visual stimuli was moderate (M = 3.80, SD = 2.00), whereas towards the tactile stimuli (M = 8.59, SD = 1.08) it was high. The pen was not perceived as threatening (M = 0.83, SD = 1.27) nor did participants report using the pen to predict the position of the tactile targets. (M = 1.81, SD = 1.71).

Mean scores on each of the RHI items for the left and right hand are displayed in Figure 5. The mean responses on the RHI items did not differ between the left and right hands (not significant). Testing the internal consistency of the 9 items, we calculated Cronbach's α and deleted items in a stepwise manner, until α was maximal. The highest internal consistency (α = 0.95) was found for a subset of 3 items (items 2, 8 and 9), compared to the complete survey (α = 0.91). Mean scores on the 3 selected items were positive (*item* 2: M = 0.22, SD = 1.70; *item 8*: M = 0.67 ,SD = 1.92; *item 9*: M = 0.19 ,SD = 1.94), but only item 8 was significantly different from zero (t(51) = 2.51, p < 0.05). Mean scores on the remaining items were either significantly negative (*item 3*: M = -1.09, SD = 1.68, t(51) = -4.67, p <0.001; *item 4*: M = -1.51, SD = 1.45, t(51) = -7.47, p < 0.0001; *item 5*: M = -1.29, SD = 1.60, t(51) = -5.79, p < 0.0001; *item 6*: M = -1.31, SD = 1.82, t(51) = -5.20, p < 0.0001), or did not significantly differ from zero (*item 1*: M = -0.05, SD = 1.57, t(51) = -0.25, p = 0.804; *item 7*: M = -0.32, SD = 1.64, t(51) = -1.39, p = 0.17). The three items that resulted in the highest internal consistency, i.e. items 2, 8 and 9, all reflected the extent to which participants felt that the rubber hands were their hands. In fact, these items corresponded to a subcomponent of embodiment, called *ownership*, as observed in a

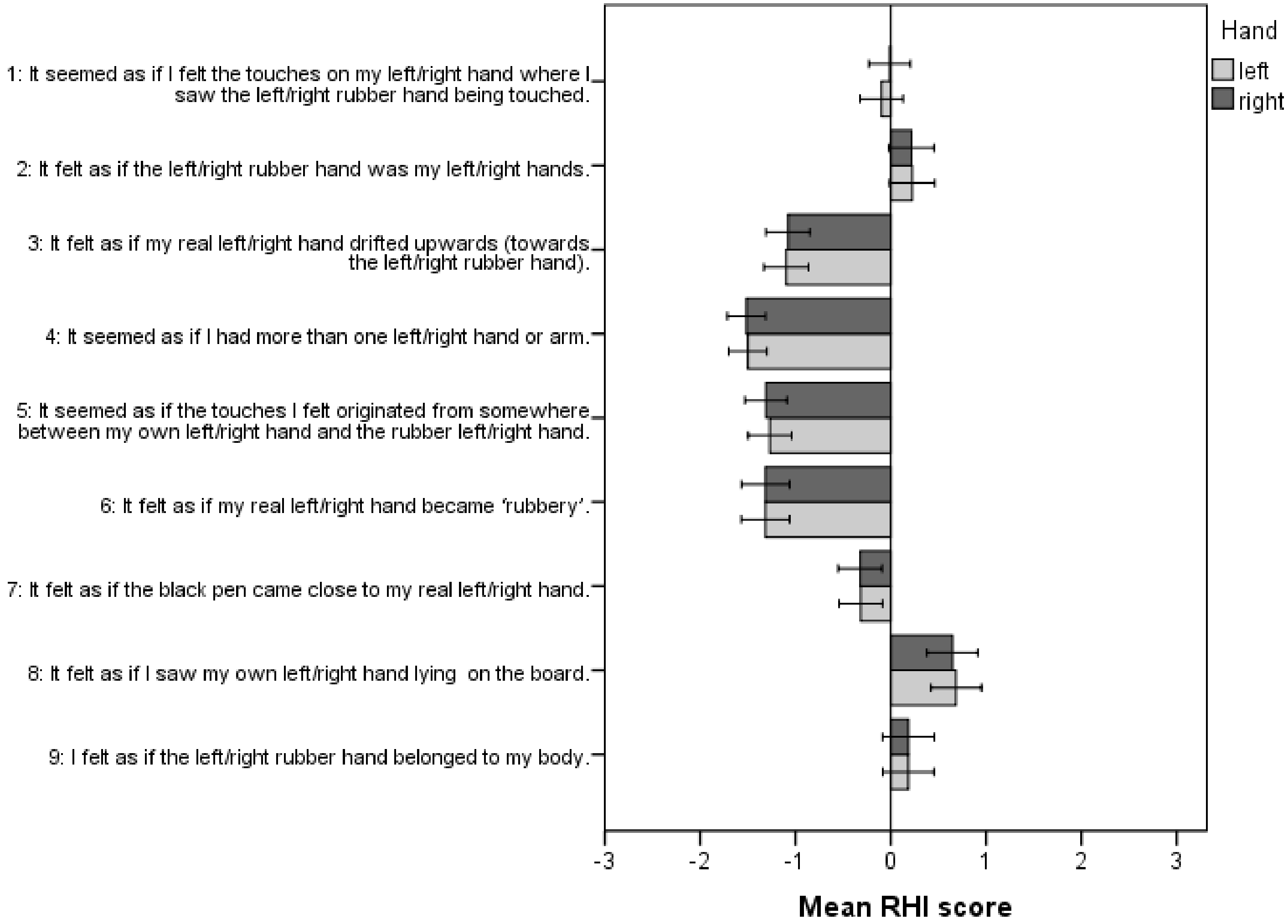

FIGURE 5. Mean scores on RHI items. Error bars represent one standard error of the mean (SEM).

psychometric analysis of RHI items (Longo, Schüür, Kammers, Tsakiris, & Haggard, 2008). According to this study, there are two other subcomponents of embodiment, namely: *location,* defined by the authors as the feeling that the rubber hand and one's own hand were in the same place and referring to sensations of causation between the seen and felt touches, and *agency*, defined by the authors as related to the feelings of being able to move the rubber hand and control over it. As none of the items used in our survey reflected agency or location, these subcomponents were not further analyzed. As a result, we decided to include only the mean score on the items reflecting the ownership subcomponent (i.e. items 2, 8 and 9) in the following analyses.

TACTILE DETECTION ACCURACY

The model that demonstrated the best fit included the main effects of the fixed factors, all two-way interactions, a random subject-based intercept, and a random effect for *Congruency*, *Intensity* and *Presence RH*.

We found a significant main effect of *Intensity* ($\chi^2(1) = 86.25$, $p < 0.001$, $\beta = -1.55$, 95% CI [-1.87 to -1.22]) showing higher *TDA* on high intensity trials ($M = 0.85$, 95% CI [0.79 to 0.89]) than on low intensity trials ($M = 0.60$, 95% CI [0.53 to 0.67]). There was also a significant main effect of *Congruency* ($\chi^2(1) = 17.46$, $p < 0.001$, $\beta = -0.57$, 95% CI [-0.84 to -0.30]), suggesting that participants were significantly more accurate on congruent trials ($M = 0.73$, 95% CI [0.67 to 0.78]) than on incongruent trials ($M = 0.62$, 95% CI [0.54 to 0.69]). The main effect of *Presence RH* was not significant ($\chi^2(1) = 0.02$, $p = 0.89$, $\beta = 0.02$, 95% CI -0.26 to 0.30]). There was a significant interaction effect between *Congruency* and *Presence RH* ($\chi^2(1) = 7.39$, $p = 0.007$, $\beta = -0.26$, 95% CI [-0.44 to -0.07]) (Figure 6). Further investigation of this effect showed that there was a significant difference between congruent and incongruent trials both when the rubber hands were present (mean difference = 11.94%; $\chi^2(1) = 51.99$, $p < 0.001$) and when they were absent (mean difference = 7.33%; $\chi^2(1) = 21.20$, $p < 0.001$). No significant difference was found between trials on which the rubber hands were present and trials on which they were absent for congruent ($\chi^2(1) = 2.10$, $p = 0.15$), nor for incongruent ($\chi^2(1) = 1.11$, $p = 0.29$) trials.

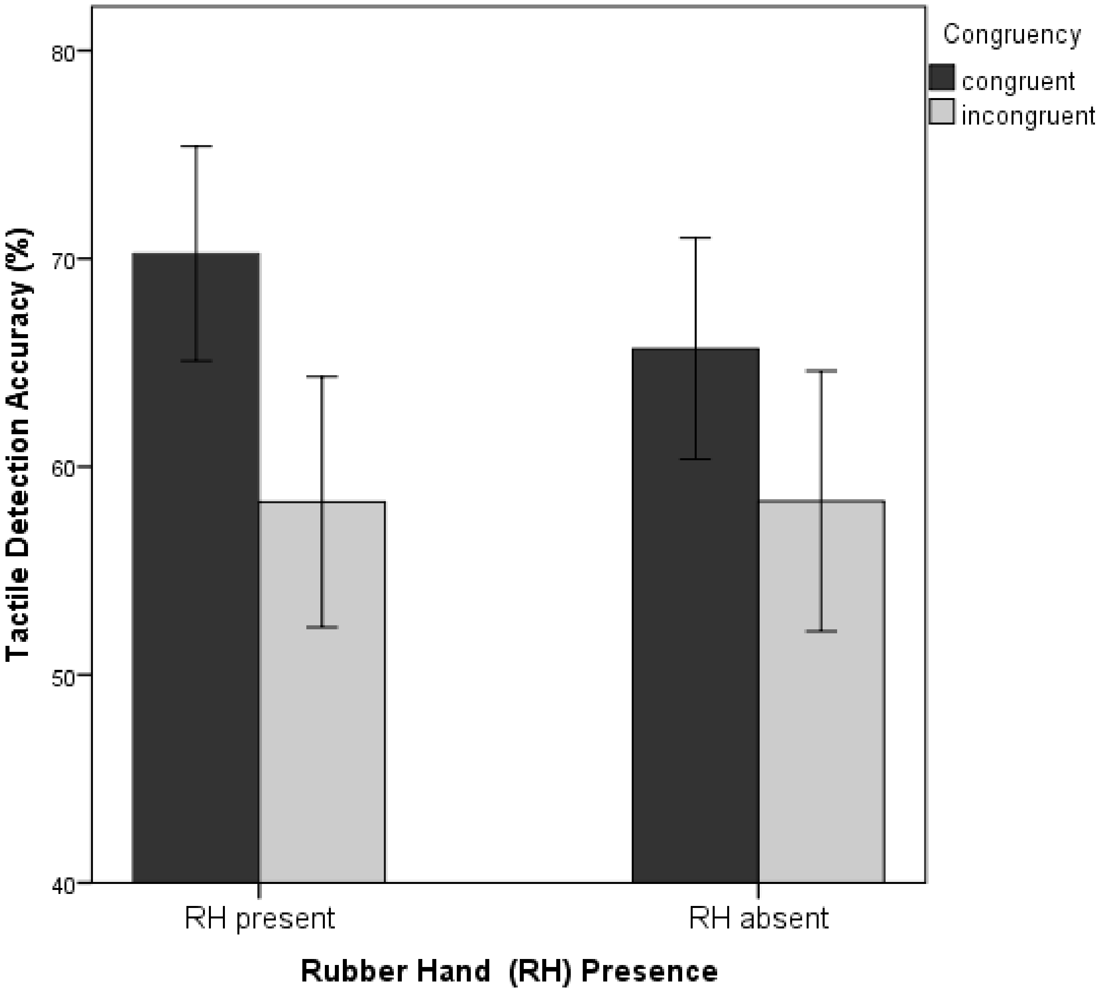

FIGURE 6. Tactile Detection Accuracy (%) in each condition. Error bars represent two standard errors of the mean (SEM)

There was also a significant interaction effect between *Intensity* and *Presence RH* ($\chi^2(1) = 4.63$, $p = 0.03$, $\beta = 0.26$, 95% CI [0.02 to -0.51]). Further investigation showed that participants were significantly less accurate on low intensity trials than on high intensity trials, both when rubber hands were present ($\chi^2(1) = 61.00$, $p < 0.001$), and when they were absent ($\chi^2(1) = 89.44$, $p < 0.001$). Interestingly, for low intensity trials, participants were more accurate when hands were present, than when they were absent, although this difference was only marginally significant ($\chi^2(1) = 3.41$, $p = 0.06$). For high intensity trials, there was no significant difference in *TDA* between trials in which the rubber hands were present, and trials in which they were absent ($\chi^2(1) = 0.71$, $p = 0.40$). Finally, the interaction effect between *Congruency* and *Intensity* was marginally significant ($\chi^2(1) = 3.59$, $p = 0.06$, $\beta = 0.24$, 95% CI [-0.008 to -0.48]). Follow-up tests indicate that participants were more accurate on high than on low intensity trials both for congruent ($\chi^2(1) = 83.89$, $p < 0.001$) and incongruent trials ($\chi^2(1) = 65.08$, $p < 0.001$). Moreover, the difference between congruent and incongruent trials was significant both for high ($\chi^2(1) = 29.82$, $p < 0.001$) and low ($\chi^2(1) = 34.39$, $p < 0.001$) intensity trials.

When the scores on the RHI survey (i.e. *Ownership*) were added to the model as a covariate factor, the best fit included the main effects of the fixed factors, and all interactions between each of the factors (up to the four-way interaction), a random subject-based intercept, and a random effect for *Congruency*, *Intensity* and *Presence RH*.

There was a significant main effect of *Congruency* ($\chi^2(1) = 8.12$, $p = 0.004$, $\beta = -0.48$, 95% CI [-0.81 to -0.15]), indicating a *TDA* for congruent ($M = 0.73$, 95% CI [0.67 to 0.78]) than for incongruent ($M = 0.62$, 95% CI [0.54 to 0.69]) trials. There was also a significant main effect of *Intensity* ($\chi^2(1) = 69.92$, $p < 0.001$, $\beta = -1.49$, 95% CI [-1.84 to -1.14]), showing a higher *TDA* on high ($M = 0.85$, 95% CI [0.79 to 0.89]) than on low ($M = 0.60$, 95% CI [0.53 to 0.67]) intensity trials. The main effect of *Presence RH* was not significant ($\chi^2(1) = 0.50$, $p = 0.48$, $\beta = 0.13$, 95% CI [-0.23 to 0.48]), nor was the main effect of *Ownership* ($\chi^2(1) = 0.14$, $p = 0.71$, $\beta = -0.04$, 95% CI [-0.29 to 0.20]). The interaction between *Congruency and Presence RH* was also significant ($\chi^2(1) = 4.06$, $p = 0.04$, $\beta = -0.44$, 95% CI [-0.87 to -0.01]). Further investigation of this effect showed that there was a significant difference between congruent and incongruent trials both when the rubber hands were present ($\chi^2(1) = 50.00$, $p < 0.001$) and when they were absent ($\chi^2(1) = 15.63$, $p < 0.001$). Interestingly, for congruent trials participants were more accurate when rubber hands were present than when they were absent, although this difference was only marginally significant ($\chi^2(1) = 3.02$, p = 0.08). For incongruent trials, the presence of the rubber hands did not influence accuracy ($\chi^2(1) = 0.53$, p = 0.20). Finally, a marginally significant four-way interaction was found between *Congruency, Presence RH, Intensity and Ownership* ($\chi^2(1) = 3.64$, $p = 0.056$, $\beta = 0.26$, 95% CI [-0.007 to 0.53]). To further investigate this effect, a separate model was fit for low and high intensity trials.

For **low intensity** trials, the best fitting model included the main effects of the fixed factors, and the interaction between *Congruency and Presence RH*, a random subject-based intercept, and a random effect for *Congruency* and *Presence RH*. There was a significant main effect of *Congruency* ($\chi^2(1) = 15.02$, $p < 0.001$, $\beta = -0.36$, 95% CI [-0.54 to -0.18]), indicating that participants were more accurate on congruent ($M = 0.65$, 95% CI [0.59 to 0.72]) than on incongruent trials ($M = 0.54$, 95% CI [0.47 to 0.62]). Furthermore, a main effect of *Presence RH* appeared ($\chi^2(1) = 7.72$, $p = 0.005$, $\beta = 0.27$, 95% CI [0.08 to 0.45]), indicating that participants were more accurate when the rubber hands were present ($M = 0.62$, 95% CI [0.55 to 0.68]), than when they were absent ($M = 0.58$, 95% CI [0.50 to 0.66]). The main effect of *Ownership* was still not significant ($\chi^2(1) = 0.22$, $p = 0.64$, $\beta = -0.04$, 95% CI [-0.20 to 0.12]). Finally, the interaction effect between *Congruency and Presence RH* was significant ($\chi^2(1) = 4.25$, $p = 0.04$, $\beta = -0.22$, 95% CI [-0.42 to -0.01]). Follow-up contrasts indicated that there was a significant difference between congruent and incongruent trials both when hands were present ($\chi^2(1) = 38.40$, $p < 0.001$) and when they were absent ($\chi^2(1) = 15.02$, $p < 0.001$). However, for congruent trials there was now a significant difference in *TDA* between trials on which the rubber hands were present and trials on which they were absent ($\chi^2(1) = 7.72$, $p = 0.01$). For incongruent trials, this difference was not significant ($\chi^2(1) = 0.29$, $p = 0.59$).

For **high intensity** trials, the best fitting model included the main effects of the fixed factors, and all the interactions (up to the three-way interaction), and a random subject-based intercept. There was a significant main effect of *Congruency* ($\chi^2(1) = 12.34$, $p < 0.001$, $\beta = -0.54$, 95% CI [-0.83 to -0.24]), indicating a higher *TDA* for congruent ($M = 0.89$, 95% CI [0.84 to 0.92]) than for incongruent ($M = 0.79$, 95% CI [0.72 to 0.84]) trials. The main effect of *Presence RH* ($\chi^2(1) = 1.70$, $p = 0.19$, $\beta = 0.22$, 95% CI [-0.11 to 0.53]) and the main effect of *Ownership* ($\chi^2(1) = 0.10$, $p = 0.76$, $\beta = -0.04$, 95% CI [-0.27 to 0.19]) were not significant. The interaction effect between *Congruency and Presence* was significant ($\chi^2(1) = 4.06$, $p = 0.04$, $\beta = -0.43$, 95% CI [-0.86 to -0.01]). Follow-up tests showed that there was a significant difference between congruent and incongruent trials, both when the rubber hands were present ($\chi^2(1) = 38.91$, $p < 0.001$), and when they were absent ($\chi^2(1) = 12.34$, $p < 0.001$). The difference between trials in which the rubber hands were present and trials in which they were absent was not significant, nor for congruent ($\chi^2(1) = 1.70$,

p = 0.19), nor for incongruent ($\chi^2(1)$ = 2.49, p = 0.11) trials. Finally, the three-way interaction between *Congruency, Presence and Ownership* was marginally significant ($\chi^2(1)$ = 3.05, p = 0.08, β = -0.22, 95% CI [-0.46 to 0.03]). Inspection of the interaction effect shows that while *Ownership* score doesn't really seem to influence *TDA* when the rubber hands are absent, it does seem to influence *TDA* when rubber hands are present. On congruent trials accuracy increases with increasing *Ownership*, whereas on incongruent trials *TDA* decreases with increasing *Ownership*. A follow-up test confirms that the slopes for *Ownership* are not significantly different between congruent and incongruent trials when rubber hands are absent ($\chi^2(1)$ = 0.27, p = 0.60), but they are significantly different between congruent and incongruent trials when rubber hands are present ($\chi^2(1)$ = 3.75, p = 0.05).

DISCUSSION

The aim of this study was to investigate the role of vision, irrespective of proprioception, in the context of somatosensory perception. By using fake rubber hands, aligned realistically in front of participants, we created a dissociation between visual and proprioceptive information on hand position. As such we could investigate whether *seeing* your hands being approached or *feeling* your hands near the approaching movement (i.e. proprioception) influences tactile perception. We hypothesized that visually approaching the participants' hands, hidden from sight, would increase tactile sensitivity of the approached hand; especially when rubber hands were visible, in particular in participants reporting a high degree of embodiment. In summary, there were four main findings in this study. First, approaching participants' *unseen* hands did increase tactile detection accuracy (TDA) of the approached hand. Second, this *visuo-tactile congruency effect* was even stronger when rubber hands were approached. Third, simply seeing the rubber hands improved TDA in trials with stimuli of sub-threshold intensity, regardless of which hand (congruent or incongruent) was approached. Finally, participants reported some feelings of ownership towards the rubber hands, but the modulatory role of embodiment in the effect of the rubber hands remained unclear.

The observed *visuo-tactile congruency effect* is in line with crossmodal spatial cueing studies demonstrating the effect of visual cues (Driver & Spence, 1998; Eimer, 2001; Macaluso & Driver, 2001; Spence et al., 1998), or more specifically, *approaching* visual cues (Graziano et al., 1994; Kandula, Hofman, & Dijkerman, 2015; Van der Biest et al., 2016) on tactile perception. Remarkably, the effect was also quite strong when rubber hands were absent ($p < 0.001$). Given the size of the *visuo-tactile congruency effect*, a ceiling effect in the condition with rubber hands might explain why the visuo-tactile congruency effect in the absence of rubber hands was only somewhat lower (7.33% vs. 11.94%). Aside from this possibility, simply viewing the experimenter approaching a region of space, known to be close to the left or right hand through proprioceptive knowledge, could already have caused the visuo-tactile interaction by itself (i.e. improved spatial orienting). The fact that the *visuo-tactile congruency effect* was still stronger when rubber hands were present, is in agreement with the study of Pavani et al. (2000) in which the effect of congruency between visual cues (LEDs) and tactile two-point discriminations was also stronger when two rubber hands were presented in a realistic position.

It was also found that mere presence of rubber hands marginally improved TDA in trials with stimuli of sub-threshold intensity ($p = 0.06$), but not in trials with stimuli of supra-threshold intensity ($p = 0.40$). This is consistent with studies demonstrating that mere vision of body-parts enhances tactile perception, also referred to as the visual enhancement of touch (VET) effect (Haggard et al., 2003; Kennett, Taylor-Clarke, & Haggard, 2001). According to Haggard, Christakou and Serino (2007), this VET effect can be explained by the sharpening of tactile receptive fields when viewing the body. The observation of the VET effect in trials with stimuli of sub-threshold intensity only, is in line with the *inverse efficiency effect*, as first described by Stein and Meredith (1993). These authors initially stated that multisensory enhancement is maximal when stimuli are near the sensory threshold. Other authors (Press et al., 2004) later added that VET effects are positively related to the difficulty of the task. Likewise, in the current study, TDA while seeing rubber hands was higher when the difficulty of the task was the highest (i.e. sub-threshold intensity, as opposed to supra-threshold intensity). Unlike many studies investigating the VET effect, in our study, participants did not see their own hands, but fake counterparts, positioned realistically relative to their upper body. Although some authors have attributed a specific role to the processing of seeing one's *own* body regarding VET effects (Longo, Cardozo, & Haggard, 2008), other studies also found comparable effects from seeing other than self-belonging body-parts, such as rubber hands (Pavani et al., 2000; Wesslein et al., 2014) or the experimenter's arm (Haggard, 2006).

These studies, amongst others (Botvinick & Cohen, 1998; Pavani et al., 2000; Wesslein et al., 2014), indicate that a sense of belonging or of embodiment with fake body-parts might be essential in the effect of rubber hands on somatosensory perception. Accordingly, we expected that the effect of approaching fake hands would depend on the extent to which participants identified the rubber hands as belonging to their own body. Results from the RHI questionnaire revealed that participants in this study did experience a sense of ownership towards the rubber hands, comparable to reports from similar studies (Longo, Schüür, et al., 2008; Wesslein et al., 2014). The role of ownership in the effect of rubber hands presence on TDA was however inconsistent in our study. In trials with stimuli of supra-threshold intensity, ownership modulated the effect of rubber hands presence on TDA, namely: in congruent trials, greater ownership with the rubber hands led to higher TDA, whereas in incongruent trials, ownership deteriorated TDA. In trials with stimuli of sub-threshold intensity or when the rubber hands were not present, no modulatory effect of ownership was found. Although the current results suggest some involvement of ownership with fake hands in the effect of vision on touch, future studies should include more items to measure embodiment according to its multiple subcomponents.

The standard procedure of installing the rubber hand illusion (RHI) was not used in this study. Normally, the RHI is induced by simultaneously stroking the participant's *unseen* hand and its fake counterpart, causing a correlation between visual stimulation of the fake hand and tactile stimulation of the real hand (Botvinick & Cohen, 1998; Tsakiris & Haggard, 2005). Due to the set-up of this experiment (metal board above the participant's hands), the experimenter was impeded to perform this procedure. However, there is evidence from at least two other studies that correlated visuo-tactile stimulation is not necessary to elicit the illusion (Farnè, Pavani, Meneghello, & Làdavas, 2000; Pavani et al., 2000). In fact, Longo, Cardozo and Haggard (2008) state that there are two independent pathways to the emergence of the rubber hand illusion: one driven by the synchronous stroking of the participant's hands and a fake hand, and one based on visual perception of the rubber hand in a realistic position and orientation. In the first case, synchronous stroking is believed to create a 'multisensory synchrony effect' which would cause participants to attribute the fake hand to their own body (cf. *self-specific* body image explanation). In the second case, the RHI is explained by the mere visual recognition of the characteristic structural form of a hand, and is therefore not recognized as genuine crossmodal integration (cf. *generic* body image explanation).

According to these theoretical accounts, the effect of the rubber hands would in this study be explained by the participants' visual recognition of the rubber hands as actual hands, and not by an attribution of the fake hands to the self. However, one other explanation is that the partial (0.25 or 0.50 when including bilateral target trials) – but perfectly synchronous – correlation between the tapping of the rubber hands with the pen and the tactile stimuli on the same location of the real hands served as a kind of synchronous stroking and caused a multisensory synchrony effect. The rubber hands would then have been attributed to the self (cf. the self-specific body image explanation). As self-reports on embodiment are neither low nor high, it remains unsure which of these mechanisms underlay the effect of approaching rubber hands on tactile processing, found in this study.

There were some limitations to this study. First, unlike the study of Pavani et al. (2000), no follow-up experiment was conducted to control for the position of the rubber hands (realistic versus unrealistic). Although we expect the effect of approaching rubber hands on tactile perception to be smaller when the rubber hands are misaligned (see Pavani et al., 2000), a follow-up experiment would be needed to confirm this hypothesis. Second, the standard procedure of inducing the RHI was not used in this study. However, various studies indicate that the RHI can also arise from the visual recognition of the fake hands as real hands, based on structural and positional characteristics. Third, as there is not yet a validated questionnaire for assessing embodiment in the RHI studies, it is possible that the limited set of items in our RHI survey did not capture the full experience of the rubber hand illusion.

In conclusion, this study corroborates evidence on the enhancing effect of viewing the body, even realistically aligned artificial body-parts, on tactile perception. In addition, it shows that earlier findings on visual capture of touch when viewing fake body-parts can be generalized to visual stimuli that are dynamic (i.e. approaching the participant) rather than static, underlining the robustness of the effect for more real-life resembling stimuli. Finally, the results from this study are in line with recent theoretical accounts on the role of vision in locating the position of touch in (near) space, through the spatial remapping of somatosensory stimuli to external visuospatial coordinates.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest related to the present study.

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APPENDIX

Model	Test	Random	AIC	Df	χ^2	*p*-value
1	Initial fit	1	11253	9		
2	Random Congruency (1 vs. 2)	1 + Congruency	11228	11	$\chi^2(2) = 28.80$	<0.001
3	Random Congruency and Presence (2 vs. 3)	1 + Congruency + Presence	11190	14	$\chi^2(3) = 43.96$	<0.001
4	Random Congruency, Presence and Intensity (3 vs. 4)	1 + Congruency + Presence + Intensity	11092	18	$\chi^2(4) = 106.29$	<0.001

TABLE 1. Step 1. Determine random effects structure, all models have 'subject' as random intercept. Decision: random effect for Congruency, Presence and Intensity added: keep model 4.

Model	Test	Fixed	AIC	Df	χ^2	*p*-value
1	Initial fit	Congruency * Intensity * Presence	11092	18		
2	Remove three-way interaction (1 vs. 2)	Congruency * Intensity + Congruency * Presence + Intensity * Presence	11090	17	$\chi^2(1) = 0.80$	0.37
3	Remove interaction with presence (2 vs. 3)	Congruency * Intensity + Presence	11099	15	$\chi^2(2) = 12.61$	0.002
4	Remove interaction with intensity (2 vs. 4)	Congruency * Presence + Intensity	11095	15	$\chi^2(2) = 8.40$	0.01
5	Remove interaction with congruency (2 vs. 5)	Presence * Intensity + Congruency	11097	15	$\chi^2(2) = 10.98$	0.004

TABLE 2. Step 2. Determine fixed effects – Trim down the model. Decision: choose model 2 without the three-way interaction.

Effects	***B***	**SE(B)**	χ^2	Df	*p*
Intercept	2.05	0.21	93.12	1	<0.001
Congruency	-0.57	0.14	17.46	1	<0.001
Intensity	-1.55	0.17	86.25	1	<0.001
Presence	0.02	0.14	0.02	1	0.89
Congruency * Intensity	0.24	0.12	3.59	1	0.06
Congruency * Presence	-0.26	0.09	7.39	1	0.007
Intensity * Presence	0.27	0.12	4.63	1	0.03

TABLE 3. Step 3. Test final model.

Model	Test	Random	AIC	Df	χ^2	*p*-value
1	Initial fit	1	11263	17		
2	Random Congruency (1 vs. 2)	1 + Congruency	11239	19	$\chi^2(2) = 28.14$	<0.001
3	Random Congruency and Presence (2 vs. 3)	1 + Congruency + Presence	11201	22	$\chi^2(3) = 43.76$	<0.001
4	Random Congruency, Presence and Intensity (3 vs. 4)	1 + Congruency + Presence + Intensity	11103	26	$\chi^2(4) = 106.38$	<0.001

TABLE 4. Step 1. Determine random effects structure, all models have 'subject' as random intercept. Decision: random effect for Congruency, Presence and Intensity added: keep model 4.

Model	Test	Fixed	AIC	Df	χ^2	*p*-value
1	Initial fit	Congruency * Intensity * Presence * RHI	11103	26		
2	Remove four-way interaction (1 vs. 2)	Congruency * Intensity * Presence + Congruency * Presence * RHI + Congruency * Intensity * RHI + Intensity * Presence * RHI	11090	25	$\chi^2(1) = 3.62$	0.057

TABLE 5. Step 2. Determine fixed effects – Trim down the model. Decision: choose model 1 with the four-way interaction.

Effects	***B***	**SE(B)**	χ^2	Df	*p*
Intercept	2.00	0.22	84.09	1	<0.001
Congruency	-0.48	0.17	8.12	1	0.004
Intensity	-1.49	0.18	69.92	1	<0.001
Presence	0.13	0.18	0.50	1	0.48
RHI	-0.05	0.12	0.14	1	0.71
Congruency * Intensity	0.13	0.17	0.54	1	0.46
Congruency * Presence	-0.44	0.22	4.06	1	0.04
Congruency * RHI	0.06	0.10	0.35	1	0.55
Intensity * Presence	0.14	0.18	0.57	1	0.45
Intensity * RHI	0.04	0.10	0.13	1	0.72
Presence * RHI	0.11	0.10	1.09	1	0.30
Congruency * Intensity * Presence	0.22	0.24	0.83	1	0.36
Congruency * Intensity * RHI	-0.11	0.10	1.33	1	0.25
Congruency * Presence * RHI	-0.21	0.13	2.76	1	0.10
Intensity * Presence * RHI	-0.15	0.10	2.10	1	0.15
Congruency * Intensity * Presence * RHI	0.26	0.14	3.64	1	0.06

TABLE 6. Step 3. Test final model.

PART II

CHAPTER 4

AN APPROACHING OBJECT THAT SIGNALS PAIN DISRUPTS VISUO-TACTILE INTERACTIONS[4]

ABSTRACT:

That pain captures attention and interrupts ongoing tasks is well-known from a wealth of studies. However, less is known about how stimuli that signal pain affect the processing of stimuli in other modalities near or on the pain-threatened body-part. The aim of this study was to investigate whether a visual stimulus that approaches the body enhances the processing of tactile stimuli on the approached body-part, and to test whether this visuo-tactile interaction is stronger when the approaching stimulus is threatening – i.e. signals the occasional occurrence of a painful stimulus on the approached body-part. We tested this hypothesis in an IVAO task (N = 52) in which participants detected and localized near-threshold tactile stimuli on the hands, after being approached by a pen-like object, held by the experimenter. Approaching movements were aimed at the left or right hand, and were performed with either a yellow or blue pen, of which one color predicted the delivery of a painful stimulus on the approached hand, as instructed to participants. Tactile stimuli were administered on the approached hand (congruent unilateral target trials), on the opposite hand (incongruent unilateral target trials), on both hands simultaneously (bilateral target trials) or were absent (catch trials). Visual stimuli were unpredictive of the location of the tactile targets. Tactile Detection Accuracy (TDA), as a measure of tactile sensitivity, was calculated and expected to be higher for congruent than incongruent trials, especially when visual stimuli signaled possible pain. As such, we expected that the stimuli signaling pain would facilitate crossmodal interactions between vision and touch. The results indicated that pain anticipation interrupted task performance, especially at the approached hand. This would imply that visuo-tactile interactions are interrupted, rather than facilitated, during the anticipation of pain. The results are discussed in terms of theoretical and methodological issues.

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[4] Van der Biest, L., Legrain, V., De Paepe, A.L., Crombez, G. (unpublished manuscript). An approaching object that signals pain disrupts visuo-tactile interactions.

INTRODUCTION

Humans are in constant interaction with objects or persons in the external space. Most often these interactions are positive and functional, but some may prove harmful to the body (e.g. touching a hot stove). An important function lies within recognizing and processing those stimuli that threaten the body's integrity. Pain, given its function of signaling potential tissue damage (IASP, 2012), is inherently threatening and therefore highly relevant to be processed and reacted upon. Indeed, many studies have shown that painful stimuli capture and prioritize attention and urge escape (Eccleston & Crombez, 1999). Besides the interruptive function of pain, pain seems also to increase the processing of stimuli in other modalities that are present at the same location in space (i.e. crossmodal threat-related bias). For example, Van Damme, Crombez and Lorenz (2007a) observed that the detection of visual stimuli on the wrists of healthy participants was enhanced when preceded by a threatening painful stimulus on the same wrist, compared to the opposite wrist.

Threat-related biases have also been observed for non-painful stimuli (e.g. Koster, Crombez, Verschuere, Van Damme, & Wiersema, 2006; Lloyd, Morrison, & Roberts, 2006; Öhman, Flykt, & Esteves, 2001). Although each sensory modality is capable of signaling threat or impending pain (e.g. *smelling* gas, *hearing* a growling dog, or *tasting* something poisonous), most studies have focused on the visual domain (e.g. *seeing* a snake). For instance, detection of visual discrepancies was faster for fear-relevant pictures (snakes or spiders) than for fear-irrelevant pictures (flowers or mushrooms) in a visual search task (Öhman et al., 2001). Moreover, exogenous cueing studies found that threatening visual stimuli can also enhance processing of somatosensory stimuli (i.e. *crossmodal* threat-related bias). For example, in a study by Poliakoff (2007), performance on a speeded tactile discrimination (low/high frequency vibrations) task was better when preceded by a visual stimulus at the same versus the opposite hand, especially when the visual stimulus was threatening (e.g. picture of spider) as opposed to non-threatening (e.g. picture of mushroom). Similarly, Van Damme, Gallace, Spence, Crombez and Moseley (2009) found a shift in attention for tactile stimuli on the hands towards the position of threatening pictures (near the left or right hand), especially when these pictures illustrated physical threat, compared to general threat or no threat. Taken together, both painful and non-painful stimuli may cause crossmodal effects on the processing of stimuli in other modalities, when they share the same spatial coordinates, and even more so when they are threatening.

Although insights on crossmodal threat-related biases have been provided by the abovementioned studies, there are some methodological limitations. First, the threatening stimuli used in these experimental paradigms – i.e. mostly pictures of threatening events or threatening words – were usually not associated with a painful stimulus and, as such, did not pose an actual threat to the body. It has been suggested that this might explain why, in recent meta-analyses, effect sizes of threat-related biases were smaller than would be expected (Crombez, Van Ryckeghem, Eccleston, & Van Damme, 2013). Some authors have tried to overcome this issue by developing paradigms in which a task-irrelevant stimulus, or cue, signals the actual occurrence of a painful stimulus during the task (Durnez & Van Damme, 2015; Koster, Crombez, Van Damme, Verschuere, & De Houwer, 2004; Vanden Bulcke, Crombez, Durnez, & Van Damme, 2015; Vanden Bulcke, Crombez, Spence, & Van Damme, 2014; Vanden Bulcke, Van Damme, Durnez, & Crombez, 2013) and have demonstrated that such threatening stimuli are able of capturing and holding attention. However, no conclusive evidence for *crossmodal* threat-related biases has been provided by these studies. For example, in the studies of Vanden Bulcke and colleagues, shifts in both tactile (Vanden Bulcke et al., 2013) and visual (Vanden Bulcke et al., 2015) attention were observed at a threatened location (left or right hand), compared to a non-threatened location (opposite hand), but only when a visual cue (one of two colors) in front of participants indicated that a painful stimulus might follow at the threatened location (see also Durnez & Van Damme, 2015; Van Hulle, Durnez, Crombez, & Van Damme, 2015). However, this provided no evidence for crossmodal interactions as there was no spatial congruency between the visual cue and the target stimuli (see Filbrich, Torta, Vanderclausen, Azañón, & Legrain, 2016; Van Damme, Vanden Bulcke, Durnez, & Crombez, 2016). As such, convincing evidence is lacking for crossmodal biases that are modulated by the anticipation of pain.

Second, the stimuli used to induce threat are mostly static, whereas real-life threats are generally moving or even approaching the body. Several studies suggest that moving stimuli capture attention and interrupt ongoing tasks more easily than static stimuli (Carretié et al., 2009; Huang, Chen, Tran, Holstein, & Sereno, 2012; Sagliano, Cappuccio, Trojano, & Conson, 2014; Von Mühlenen, Rempel, & Enns, 2005). Especially stimuli approaching the body might be particularly relevant when aiming to protect the body, because approaching stimuli signal an object impacting the body and possibly even harming it. Various studies reported evidence of approaching stimuli interrupting ongoing tasks (Franconeri & Simons, 2003, 2005; Sagliano et al., 2014) but also enhancing tactile processing at the approached location (Canzoneri, Magosso, & Serino, 2012; Gray & Tan, 2002). Moreover, a spatio-temporal predictive link between visual stimuli approaching the body and tactile consequences has been reported in two similar studies (Cléry, Guipponi, Odouard, Wardak, & Ben Hamed, 2015; Kandula, Hofman, & Dijkerman, 2015) in which tactile processing was enhanced at the expected location and time of impact of an approaching visual stimulus. Recently, existence of a visual predictive link was also found for nociceptive stimuli. Speeded detection of nociceptive stimuli was faster when visual stimuli (illuminated LEDs) were presented near the hands, especially when visual stimuli approached – as opposed to receded from – the stimulated hand (De Paepe, Crombez, & Legrain, 2016).

As it is believed that the purpose of such predictive links is to protect the body from harm, we might expect that they are modulated by the threat value of the approaching stimulus (Carretié et al., 2009; Sagliano et al., 2014). A recent study confirmed this hypothesis for visuo-tactile interactions (de Haan, Smit, Van der Stigchel, & Dijkerman, 2016). The authors observed faster detection of tactile stimuli on the hand when presented with a nearby approaching visual stimulus, especially when it was threatening (picture of spider versus butterfly), but only when participants were afraid of the threatening stimulus. Still, only a minority of spatial attention studies have used (dynamic) visual stimuli that resemble real-life situations. Most studies have simulated movement of visual stimuli by successively illuminating LEDs or by enlarging the visual objects on a monitor. In contrast, Van der Biest, Legrain, De Paepe and Crombez (2016) used a neutral object, held by the experimenter, that approached the participant's body and found that it increased the detection of tactile stimuli at the approached body-part, especially when the approaching movement was close to the body.

Taken together, no study has yet investigated how pain anticipation modulates the effect of approaching visual stimuli on tactile processing while addressing the methodological issues discussed in the previous paragraphs, that is: *i)* using stimuli that pose an actual threat to the body by signaling the occurrence of painful stimuli; *ii)* the use of dynamic (approaching), rather than static stimuli; and *iii)* the use of visual stimuli that more resemble real-life sensory events. In this study, we attempted to meet these criteria and hypothesized that an approaching stimulus that signals the occurrence of pain will enhance tactile processing at the approached body-part to a larger extent than an approaching stimulus that does not predict pain.

In the In Vivo Approaching Object (IVAO) paradigm, participants detected and localized near-threshold vibrotactile stimuli (= targets), administered on the hands after being approached by the experimenter holding a blue or yellow pen (= visual cue). The approaching movement was aimed at the participant's left or right hand. One of the pens predicted, by means of instructions to the participant, the occasional occurrence of painful electrocutaneous stimuli on the approached hand. The other pen was never followed by a painful stimulus. Tactile targets could be presented on the same side as the approaching movement (congruent unilateral trials), on the opposite side (incongruent unilateral trials), on both sides (bilateral trials), or could be absent (catch trials). Tactile detection accuracy (TDA) was compared between congruent and incongruent trials, and between both pens (i.e. pain signal vs. safety signal). Based on previous crossmodal studies (Spence, Nicholls, Gillespie, & Driver, 1998; Van der Biest et al., 2016), we expected TDA to be higher in congruent trials, compared to incongruent trials. In addition we expected this visuo-tactile congruency effect to be stronger when participants were approached by the threatening pen, compared to the non-threatening pen.

METHOD

PARTICIPANTS

Fifty-six undergraduate students took part for course credits (age: *M* = 19.88; SD = 3.94; range = 17-42 years; 25 men; 4 left handed). Exclusion criteria were insufficiently corrected visual impairments, the self-report of current medical/psychiatric conditions or current medication intake affecting somatosensory sensitivity, pain complaints on the upper limbs. None of the participants had to be excluded for these reasons. However, the experiment was discontinued for three participants. One participant was not able to feel the tactile stimuli on the hands, another did not perceive the electrocutaneous stimuli as painful (even at very high intensities), For another person the study was discontinued due to apparatus failure. One participant was also excluded post-hoc due to apparatus failure. In total, 52 participants were included for further analysis (age: *M* = 19.87; SD = 4.06; range = 17-42 years; 22 men; 4 left handed). The study was approved by the Ethics Committee of Ghent University. All participants gave their written informed consent.

STIMULI AND APPARATUS

Participants sat with their hands, palms down, resting on a table (see Figure 1). Two square metal plates (± 4cm^2) were attached to the table and used as electrical contacts. The plates were positioned between the thumb and index finger of each hand, 50cm apart from each other and about 30cm from the edge of the table (near the participant's trunk). At a distance of 55cm in front of the edge of the table and on the body midline, a black fixation cross was attached to the table to prevent participants from shifting their gaze during the task. A chin wrest was used to fixate the participant's head during the experiment. Headphones with continuous white noise (46dB) were used to mask auditory stimuli from the immediate environment. The experimenter was sitting on the other side of the table, facing the participant at a distance of approximately 1 meter.

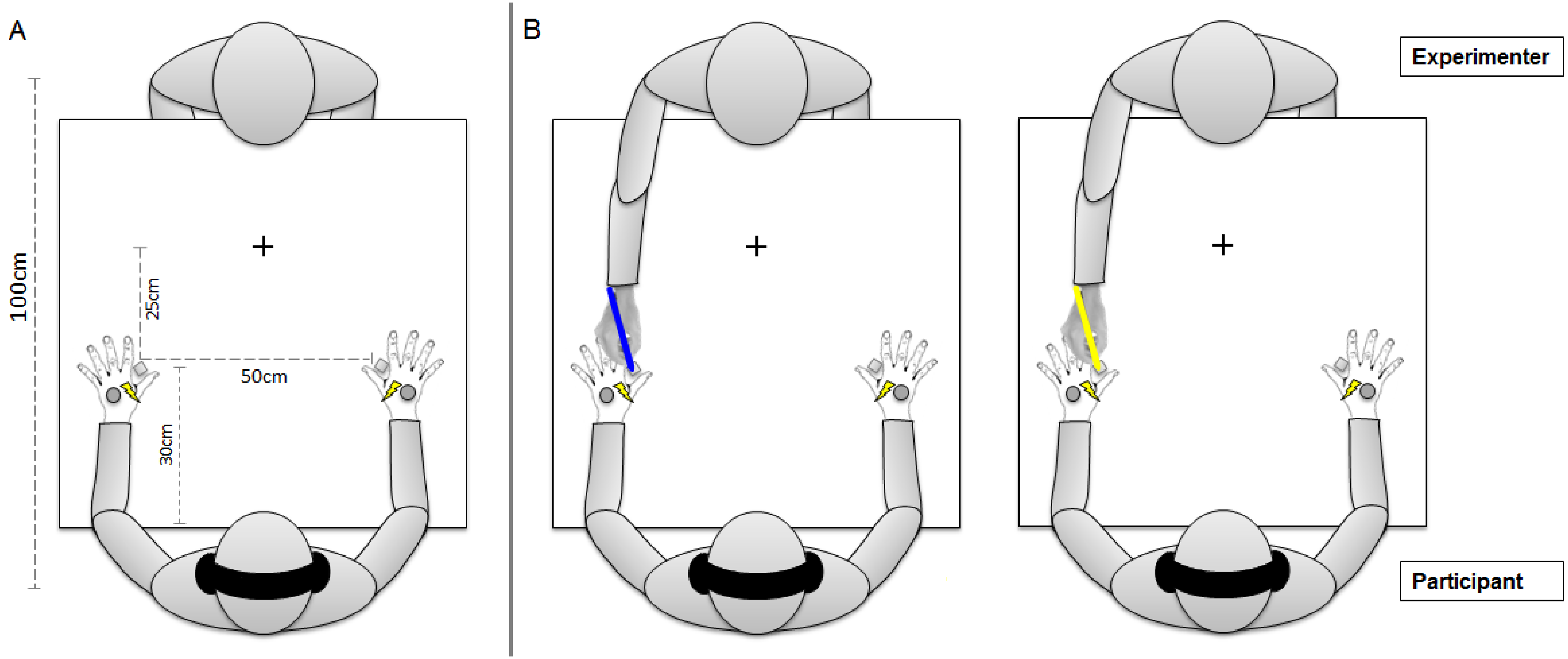

FIGURE 1. Experimental set-up of the In Vivo Approaching Object task. Panel A: Participants are seated across the experimenter with a contact plate between either thumb and index finger. Panel B: during each trial, the experimenter approaches one of the participant's hands with the blue or the yellow pen, taps the contact plate and returns to the starting position (see left panel). Tapping a contact plate with a pen triggers a vibrotactile target on the same hand, on the other hand, on both hands, or one none of the hands. Vibrotactile targets, following one of the two pens, are replaced in some trials (±10%) by an electrocutaneous stimulus on the approached hand.

VISUAL STIMULI

A blue or yellow pen was held by the experimenter and served as a visual stimulus. The experimenter held the pen and smoothly moved her arm towards one of the two metal plates and tapped it. She then moved back to the starting position of the movement. Depending on the plate that had to be approached (left or right), the arm closest to that side was used to perform the movement. The experimenter (LVDB, female) was trained to perform this movement in a standardized manner (~1s approach and ~1s retraction). Tapping the plate triggered the delivery of a tactile stimulus (after a ~2ms time interval) or an electrocutaneous stimulus.

VIBROTACTILE STIMULI

Two magnet linear actuators (C-2 TACTOR, Engineering Acoustics Inc., Casselberry, Florida) were attached to the sensory territory of the superficial radial nerve of each hand and released vibrotactile stimuli (50ms duration; 200Hz). The actuators were driven by self-developed software and a controlling device that converted electrical signals into oscillating movements of the actuators against the skin. The intensities of the vibrotactile stimuli were near the perceptual threshold, which was individually determined using an adaptive procedure. The procedure has been used in previous studies (Vandenbroucke, Crombez, Harrar, et al., 2014; Vandenbroucke, Crombez, Loeys, & Goubert, 2014). The procedure consisted of four independent yet randomly intermixed staircases of 20 trials (two series for each hand) randomly administered (80 trials in total). Each series had a starting value of 0.068Watt (W) for the first stimulus. The intensity decreased each time the participants reported feeling the stimulus, and increased when no sensation was reported. The perceptual threshold was determined for each hand, based upon the mean intensity of the last stimulus of each of the two series of that particular hand. *Supra-threshold* values were calculated for each hand by adding one fourth to the perceptual threshold.

ELECTROCUTANEOUS STIMULI

Electrocutaneous (EC) stimuli were delivered by pairs of Ag-AgCl electrodes (1cm diameter) placed on the sensory territory of the superficial radial nerve of each hand and driven by two constant current stimulators (Digitimer DS5 2000, Digitimer Ltd, UK). The electrostimulators were set at a duration of 200ms and a frequency of 50Hz. Stimulus intensity was determined for each participant by means of a staircase procedure. On each hand separately, EC stimuli of increasing intensity were administered until the pain tolerance level was achieved – i.e. when participants indicated not wanting to receive another EC stimulus of higher intensity. For each hand, the last presented stimulus (highest intensity) was selected.

SELF-REPORT MEASURES

Participants completed an anamnestic questionnaire, the Pain Grading Scale (Von Korff, Ormel, Keefe, & Dworkin, 1992), the Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995) and the Trait scale of the State-Trait Anxiety Inventory (STAI; Spielberger, 1987). The PCS and the STAI were included for a meta-analytic purposes and will therefore not be discussed in this study. A series of self-report items assessed after each block to what extent participants *i)* made an effort to perform the task; *ii)* were able to concentrated on the task; *iii)* felt tense/fearful during the task; *iv)* directed their attention towards each type of the stimuli (blue and yellow pen, tactile stimuli, EC stimuli); *v)* expected to receive a painful stimulus after seeing the blue and the yellow pen; *vi)* were fearful/tense for receiving a painful stimulus when seeing the blue and the yellow pen; *vii)* perceived the EC stimuli as painful; and *v)* found the task meaningful (i.e. not having to guess). Each item was rated using a 11-point graphic rating scale (0 = “not at all”; 10 = “very much”).

PROCEDURE

Participants completed the questionnaires and were given instructions about the staircase procedures. Headphones were turned on and participants were asked to place their chin in the chin wrest. First, the staircase procedure for vibrotactile stimuli started with a visual stimulus (a letter X, 1000ms duration) appearing in each trials in the middle of a computer screen, accompanied by a vibrotactile stimulus either on the left or right hand (position unknown to the participant). Participants verbally reported whether they had felt a vibrotactile stimulus (“yes” or “no”). Second, the staircase procedure for EC stimuli initiated. For each hand separately (random order), participants received EC stimuli of increasing order and were asked to instruct the experimenter to proceed administering stimuli for as long as they could tolerate the pain by saying “yes” after each stimulus and to stop the experimenter when they could no longer tolerate the pain by saying “stop”. Responses were manually inserted by the experimenter on a keyboard. When the staircase procedures were finished, the computer screen and the headphones were removed.

Participants were asked not to move their hands, not to touch the contact plates between their thumb and index finger and to fixate on the fixation cross during the task. In the *In Vivo Approaching Object* (IVAO) task, participants were instructed to detect a vibrotactile stimulus on the hands after being approached by the experimenter holding a blue or yellow pen (pen color equiprobable and randomized within blocks). In addition, they were told that one of the two pens, blue or yellow (counterbalanced between subjects), could occasionally result in a painful stimulus on the approached hand (left vs. right). Each trial in the IVAO task started by the experimenter approaching the participant’s left or right hand with the yellow or the blue pen (visual cue), tapping one of the contact plates near the hands and moving the pen back to its original position (near the experimenter’s trunk). Simultaneously with the tapping, a threshold or supra-threshold vibrotactile stimulus on one or both hands was triggered in 75% of the trials (target trials). In the remaining 25% of the trials, no stimulus was presented (catch trials). The vibrotactile target could be presented on the same side as the visual cue (congruent unilateral target trials), on the opposite side (incongruent unilateral target trials), or on both sides (bilateral targets trials). Participants verbally responded whether they felt a tactile stimulus, and if so, on which hand (left, right or bilaterally). In an additional 4 trials per block (EC trials), an EC stimulus was presented to the hand approached by the pen that signaled pain. In those trials, participants responded on which hand they felt the EC stimulus. The four possible responses to the target trials (“no sensation”, “left sensation”, “right sensation”, “sensations on both sides”) were manually inserted on the keyboard by the experimenter (0 = “no sensation”; 4 = “left sensation”; 6 = “right sensation”; 5 = “sensation on both sides”). Instructions about which hand to approach were visible on a computer screen in front of the experimenter but were masked from the participant’s view. The experimenter, however, was blind as to which type of trial (congruent vs. incongruent) was running.

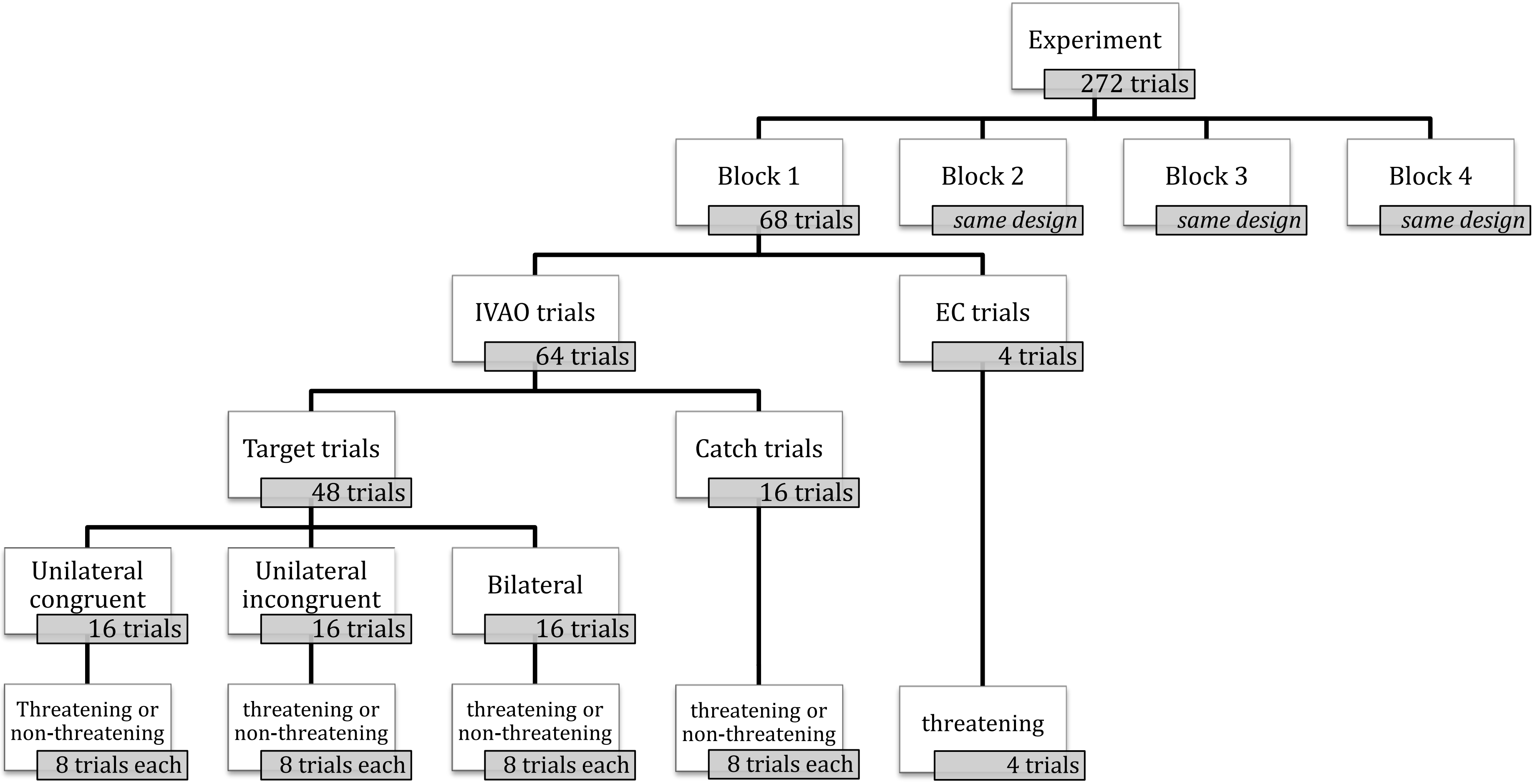

FIGURE 2. Experimental design of IVAO experiment. Intensity of tactile stimuli was below (75%) or above (25%) the perceptual threshold.

The design of the experiment is illustrated in Figure 2. In total, 272 trials was presented, divided across 4 blocks of 68 trials. Each block consisted of 64 IVAO trials (16 catch trials, 16 congruent unilateral target trials, 16 incongruent unilateral target trials and 16 bilateral target trials) and 4 EC trials. All four types of IVAO trials were presented randomly and were either threatening or non-threatening. The majority (75%) of the target trials had a stimulus of threshold intensity (i.e. 36 trials), whereas 25% had a stimulus with an intensity slightly above the perceptual threshold (i.e. 12 trials). Supra-threshold targets were presented to provide participants a sense of mastery over the task. Catch trials and bilateral trials were added to minimize strategic guessing and to maintain attention to the task. In sum, there were 8 observations (2 trials x 4 blocks) per condition for supra-threshold tactile targets and 24 observations (6 trials x 4 blocks) per condition for threshold targets. Participants completed the self-report items after each block.

ANALYSES

The outcome variable of the analysis was *Tactile Detection Accuracy (TDA)*, and was defined as the accuracy of detecting and localizing a tactile target during a trial (correct vs. incorrect). Only unilateral target trials were included in the analysis; bilateral, catch trials and EC trials were discarded. Independent variables (all within-subject variables) were the *Congruency* (congruent vs. incongruent) between visual cues and tactile targets, *Pain anticipation* (pain signal vs. safety signal) of the visual cues, the *Target Location* (left vs. right), and *Intensity* (threshold vs. supra-threshold) of the tactile targets.

A linear mixed-effects model with a logit link function, as implemented in the R package lme4 (Pinheiro & Bates, 2000) was used to analyze the effect of *Congruency, Pain anticipation*, *Intensity* and *Target Location* on *TDA*. The analysis consisted of three steps. First, all relevant factors and interactions were entered in the model as fixed factors, and a random effect was added 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 (see Appendix, Table 1). By default, a random effect was added allowing adjustments to the intercept of the *Subject* variable. In the second step, we trimmed the model to find the most parsimonious model. To achieve this, the full model was systematically restricted, comparing the goodness of fit using likelihood ratio tests and Akaike's information criterion (Hu, 2007) (see Appendix, Table 2). As we were interested in all included variables and in the interaction between *Congruency* and *Pain anticipation*, fixed effects and the two-way interaction between *Congruency* and *Pain anticipation* were never removed from the model. 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; De Ruddere, Goubert, Stevens, Amanda, & Crombez, 2013; Verbruggen, Aron, Stevens, & Chambers, 2010) (see Appendix, Table 3).

RESULTS

STAIRCASES

Perceptual thresholds for tactile stimuli did not differ between the left and the right hand (left hand: M = 0.014W, SD = 0.010; right hand: M = 0.013W, SD = 0.010; $F(1,51)$ = 1.49, p = 0.228). The intensity of the EC stimuli were somewhat higher for the right hand (M = 0.256W, SD = 0.194) compared to the left hand (M = 0.214W, SD = 0.191; $F(1,51)$ = 6.52, p = 0.014). The proportion of right handed (n = 48), compared to left handed (n = 4) participants most likely accounts for this difference (right handed: mean difference = 0.048, SD = 0.122; left handed: mean difference = -0.028, SD = 0.022), although the group of left handed participants might be too low to obtain a significant effect ($F(1,51)$ = 1.53, p = 0.222).

SELF-REPORT MEASURES

Participants reported a large amount of effort (M = 8.31, SD = 0.99) and concentration (M = 7.81, SD = 0.88) during the task and rated the task as fairly meaningful (i.e. not having to guess; M = 7.47, SD = 1.43). Fear/tension during the task was moderate (M = 4.77, SD = 2.48). The perceived pain intensity of the EC stimuli was

6.01 (SD = 2.09) and the amount of attention directed towards the EC stimuli was 6.91 (SD = 2.61). The amount of attention directed towards the tactile stimuli was 7.33 (SD = 1.63). Attention towards the pen that signaled pain (M = 5.78, SD = 2.84) was higher than attention towards the pain that signaled safety (M = 3.87, SD = 2.44; $F(1,51)$ = 53.45, $p < 0.0001$). In addition, participants expected to receive an EC stimulus more when they saw the pen that signaled pain (M = 5.27, SD = 2.84), than when they saw the pen that signaled safety (M = 1.32, SD = 2.04; $F(1,51)$ = 93.10, $p < 0.0001$) and were also more afraid to receive an EC stimulus when seeing the threatening pen (M = 5.10, SD = 2.90), as compared to the non-threatening pen (M = 1.65, SD = 2.31; $F(1,51)$ = 70.35, $p < 0.0001$).

TACTILE DETECTION ACCURACY

The model that demonstrated the best fit included the main effects of the fixed factors, the interaction between *Congruency* and *Pain anticipation*, the interaction effect between *Congruency* and *Target location,* a random subject-based intercept, and a random effect for *Congruency*, *Intensity* and *Target location*.

This model showed a significant main effect of *Intensity* ($\chi^2(1)$ = 31.33, $p < 0.001$, β = -0.93, 95% CI [-1.26 to -0.61]) with higher TDA on high intensity trials (M = 0.84, 95% CI [0.77 to 0.90]) than on low intensity trials (M = 0.68, 95% CI [0.59 to 0.76]). The main effect of *Pain anticipation* was significant ($\chi^2(1)$ = 14.91, $p < 0.001$, β = -0.34, 95% CI [-0.51 to -0.17]), indicating higher TDA on trials in which pain was signaled (M = 0.75, 95% CI [0.67 to 0.82]) than on trials in which safety was signaled (M = 0.71, 95% CI [0.62 to 0.78]). There was also a significant main effect of *Congruency* ($\chi^2(1)$ = 6.51, p = 0.01, β = -0.46, 95% CI [-0.81 to -0.11]), with higher TDA for congruent (M = 0.73, 95% CI [0.67 to 0.79]) than for incongruent (M = 0.72, 95% CI [0.61 to 0.81]) trials. The main effect of *Target location* was not significant ($\chi^2(1)$ = 0.30, p = 0.58, β = 0.15, 95% CI [-0.40 to 0.71]). The interaction effect between *Congruency* and *Target location* was significant ($\chi^2(1)$ = 15.83, $p < 0.001$, β = 0.54, 95% CI [0.27 to 0.80]). Further investigation of this effect showed that there was a significant difference between

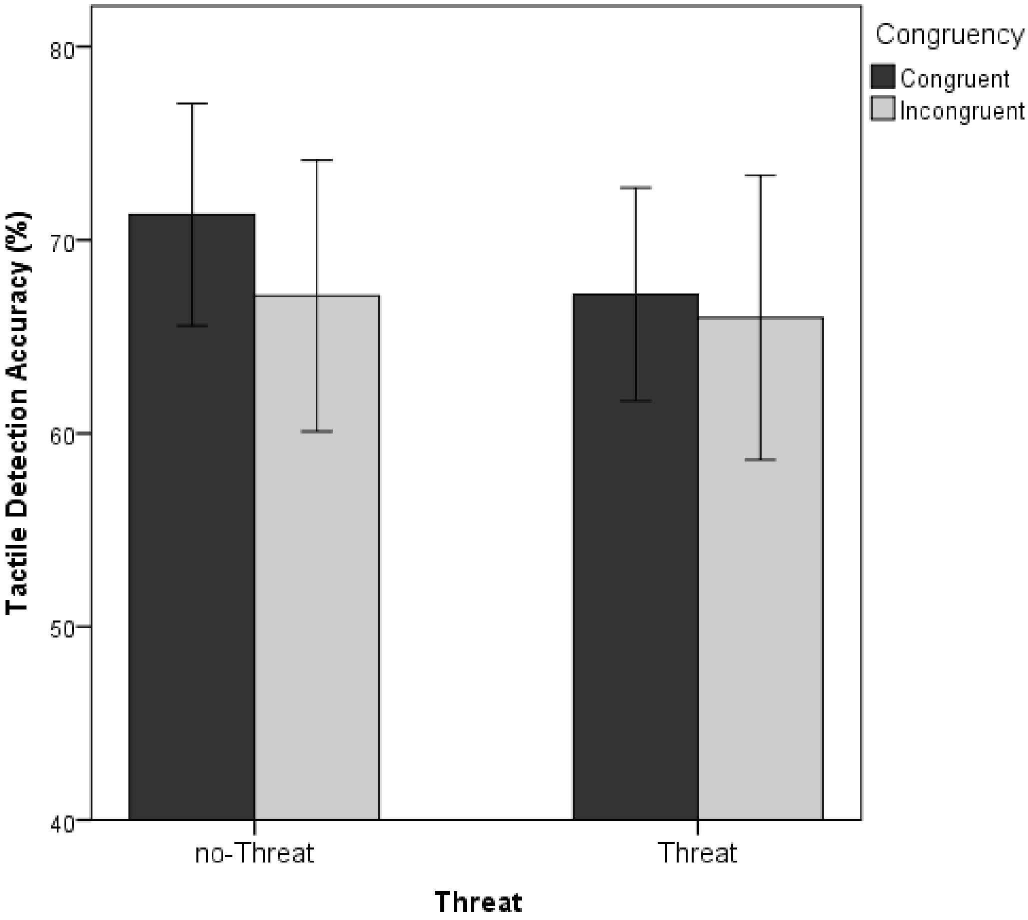

FIGURE 3. Tactile Detection Accuracy (%), depending on the pain anticipation and congruency of the visual cues. Error bars represent two standard errors of the mean (SEM)

congruent and incongruent trials when the left hand was stimulated ($\chi^2(1) = 4.04$, $p = 0.04$), but not when the right hand was stimulated ($\chi^2(1) = 1.43$, $p = 0.23$). Moreover, participants were significantly more accurate when their right hand was stimulated than when their left hand was stimulated, but only for incongruent trials ($\chi^2(1) = 5.95$, $p = 0.01$). For congruent trials the difference in TDA between left and right hand was not significant ($\chi^2(1) = 0.30$, $p = 0.58$). Finally, there was a marginally significant interaction effect between *Congruency* and *Pain anticipation* ($\chi^2(1) = 3.66$, $p = 0.06$, $\beta = 0.24$, 95% CI [-0.006 to 0.49]) (Figure 3). Further investigation of this effect showed that for congruent trials TDA was significantly higher for trials in which pain was signaled than for trials in which safety was signaled ($\chi^2(1) = 14.91$, $p < 0.001$). This difference was not significant for incongruent trials ($\chi^2(1) = 1.07$, $p = 0.30$). The difference between congruent and incongruent trials was not significant for pain signal trials ($\chi^2(1) = 1.25$, $p = 0.26$) nor for safety signal trials ($\chi^2(1) = 0.11$, $p = 0.74$).

DISCUSSION

In the current study, we aimed to investigate whether pain anticipation modulates the crossmodal effect of visual stimuli approaching the body, on tactile processing of the approached body-part. Based on previous crossmodal studies (e.g. Spence et al., 1998; Van der Biest et al., 2016), we expected that an approaching visual stimulus would enhance the detection of near-threshold tactile stimuli on the approached hand. Moreover, we hypothesized that this visuo-tactile interaction would be stronger when the visual stimulus signaled the delivery of a painful stimulus on the hand that was approached.

The expected crossmodal effect of an approaching visual stimulus on tactile processing, regardless of the signal value (pain signal vs. safety signal) of the approaching movement, was present but less pronounced than the one found in a previous study (see Van der Biest et al., 2016). The detection of tactile stimuli was higher on the approached hand compared to the opposite hand, but surprisingly, only when the tactile target was delivered on the left hand. Further investigation revealed that this smaller crossmodal effect for the right hand was caused by a higher detection of targets on the right hand in incongruent trials, thereby minimizing the difference with tactile detection on the right hand in congruent trials. Although it is unclear what might have caused this relatively high detection accuracy for right targets in incongruent trials, it cannot be due to the target intensities, as there was no difference in the perceptual threshold between left hand and right hand. Also, this would have translated in a higher detection accuracy for right hand targets *overall*, whereas in this case, this was only true for incongruent trials (i.e. when the opposite hand was approached). One might argue that the crossmodal effect is small due to the distance between the visual and tactile stimuli. Crossmodal studies have indicated that crossmodal interactions emerge when two stimuli are presented near each other (Spence, Pavani, & Driver, 2004), whereas in our study the visual stimulus was already visible at the initiation of the approaching movement. That way, the distance between the visual stimulus and tactile stimulus was quite large (~50cm) at the beginning of stimulus presentation, and only gradually decreased until the end of the approaching movement (after ~1s). However, as crossmodal effects have been found in previous studies using this paradigm (e.g. Van der Biest et al., 2016), this explanation seems very unlikely.

The modulatory effect of pain anticipation on visuo-tactile interactions was different than hypothesized. Approaching participants with the pain signaling pen did not facilitate, but rather *diminished* the detection of tactile stimuli on the approached hand. Self-report measures indicate that this was not caused by a failure in the manipulation of pain anticipation, as participants expected and were more afraid to receive a painful stimulus when they saw the pen that signaled pain than when they saw the pen that signaled safety. In what follows, several pathways are discussed through which pain anticipation could have led to diminished tactile processing on the approached hand.

First of all, the absence of facilitated crossmodal interactions in the anticipation of pain does not necessarily imply that pain signals were insufficiently attended. Participants in this study reported directing their attention more towards the visual stimuli that signaled pain than towards the visual stimuli that signaled safety, in line with previous studies (e.g. Van Damme et al., 2004; Van Damme & Legrain, 2012). As such, it could be assumed that the pain signaling movement did capture attention to a larger extent than the safety signaling movement. Still, one might wonder as to why this supposedly heightened attention towards threat did not translate in a facilitated processing of other stimuli at the expected pain location.

Of interest is the fact that the results are reminiscent of the interruptive function of pain on attentional processing, discussed earlier (Eccleston & Crombez, 1999; Pincus &

Morley, 2001). However, the seemingly interruptive effect in the current study was not caused by pain itself (i.e. EC trials were removed from analysis and did not contain tactile targets), but by the *anticipation* of receiving a painful stimulus. Although studies on the *anticipation* of pain generally report the opposite effect, namely: an increased processing of stimuli at the threatened location (Van Damme et al., 2004), there are also studies that demonstrate lower (secondary) task performance in the anticipation of pain (e.g. Dawson, Schell, Beers, & Kelly, 1982; Lipp, Siddle, & Dall, 1993). In a recent study by de Haan et al. (2016), it was suggested that difficulties disengaging from approaching visual stimuli that are threatening might delay attention to shift towards the (task-relevant) stimuli on the approached body-part.

On another account, relevant insights can also be derived from the work of Sokolov (1963), on the difference between an orienting reflex and a defensive reflex. It is argued that, when faced with stimuli of low or moderate intensity, an orienting reflex – or information processing response – is elicited that facilitates the discrimination of the sensory input. In contrast, when faced with high intensity (i.e. aversive, painful) stimuli, a defensive reflex emerges that facilitates defensive responses. Although participants in our study were restricted from any defensive movements towards the pain stimuli, a defensive reflex could have at least limited the activity of the pain signaling stimulus and thereby also inhibited discrimination of other (task-relevant) stimuli (i.e. tactile stimuli) (Sokolov, 1963). This 'breaking away from a stimulus' (Sokolov, 1963, p. 14), depends on several variables, such as stimulus intensity. Given the fact that tolerance levels were used to determine the intensity of the EC stimuli in this study, intensities might have been relatively high, compared to other staircase methods (Van der Biest, Legrain, De Paepe, & Crombez, in preparation), causing more inhibition of orienting. In addition, the intensity of the tactile stimuli was very low (i.e. near the perceptual threshold), compared to other studies (e.g. de Haan et al., 2016; Vanden Bulcke et al., 2013), implying that even small interferences with orienting could have already drastically diminished the accuracy of detecting tactile targets.

Furthermore, other cognitive factors, such as anxiety or worrying about the painful stimuli, might have disrupted task performance when faced with the pain signaling stimulus. When factors like anxiety or worrying arise while performing a task, they might distract participants and demand attention (Sarason, Pierce, & Sarason, 2014). However, the system for processing all sorts of incoming information has limited capacities, implying that attentional resources might fall short for some stimuli (e.g. task-relevant tactile stimuli) (Öhman, 1979). Although the design this study and the available data did not allow us to investigate this, we expect that certain cognitions about the painful stimuli or feelings of anxiousness might have affected task performance, and thereby also crossmodal interactions.

In sum, approaching participants' body enhanced tactile processing at the approached hand, compared to the opposite hand (i.e. visuo-tactile interaction), although less explicitly than expected. Moreover, we found that the anticipation of painful stimuli on the hands interrupted overall task performance, but especially diminished tactile processing on the hand that was approached (i.e. the hand on which pain was anticipated). As such, visuo-tactile interactions were not prevalent when being approached by an object signaling pain.

A few issues need to be considered when interpreting the results of this study. First of all, participants enrolled in this study were healthy subjects that were administered experimental pain stimuli in the lab. One should therefore be cautious in generalizing the results to chronic pain patients. Further studies using this paradigm should also address chronic pain populations. It would, for example, be intriguing to find out whether tactile processing is stronger when approached towards a (chronically) painful body-part, versus a healthy body-part. Second, it can be questioned whether the effects in this study are specific to the anticipation of pain, as there was no control condition in which non-painful somatosensory stimuli were anticipated. Although previous studies showed that attention is captured more by visual stimuli signaling painful stimuli than non-painful somatosensory stimuli (Van Damme et al., 2004; Van Damme & Legrain, 2012), our effects could, at least partly, be explained by factors, not specific to pain, such as, for example, the general arousal. Third, response mapping (left/right/both/none) was not orthogonal to stimulus presentation (left/right). Therefore, a response bias towards the approached side could have emerged, not due to perceptual processes, but due to the fact that the approached side might have been perceived as more relevant to the task. However, the fact that we found differential effects, depending on the signal value of the visual stimuli, suggests that a response bias could not fully explain the results. Participants were also never instructed to attend the approached side, nor did the visual stimulus predict the location of the subsequent tactile stimulation, expect in the few EC trials. Nevertheless, adapting the response organization, for example by making participants respond orthogonally on a foot pedal (lift toes vs. heel), could prevent response biases from confounding the results.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest related to the present study.

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APPENDIX

Model	Test	Random	AIC	Df	χ^2	*p*-value
1	Initial fit	1	7270	17		
2	Random Congruency (1 vs. 2)	1 + Congruency	7179	19	$\chi^2(2) = 94.11$	<0.001
3	Random Congruency and Threat (2 vs. 3)	1 + Congruency + Threat	7183	22	$\chi^2(3) = 2.94$	0.40
4	Random Congruency and Intensity (2 vs. 4)	1 + Congruency + Intensity	7113	22	$\chi^2(3) = 72.30$	<0.001
5	Random Congruency, Intensity and Target location (4 vs. 5)	1 + Congruency + Intensity + Target location	6488	26	$\chi^2(4) = 633$	<0.001

TABLE 1. Step 1. Determine random effects structure. All models have 'subject' as random intercept. Decision: random effect for Congruency, Intensity and Target location added: keep model 5.

Model	Test	Fixed	AIC	Df	χ^2	*p*-value
1	Initial fit	Congruency * Intensity * Threat * Target location	6488	26		
2	Remove four-way interaction (1 vs. 2)	(Congruency + Intensity + Threat + Target location)^3	6486	25	$\chi^2(1) = 0.006$	0.94
3	Remove three-way interactions (2 vs. 3)	(Congruency + Intensity + Threat + Target location)^2	6479	21	$\chi^2(4) = 0.66$	0.96
4	Remove interaction with intensity (3 vs. 4)	Congruency * Threat + Congruency * Target location + Threat * Target location + Intensity	6476	19	$\chi^2(2) = 0.97$	0.62
5	Remove all interactions with Target location (4 vs. 5)	Congruency * Threat + Target location + Intensity	6485	16	$\chi^2(3) = 15.57$	0.001
6	Remove interaction between Threat and Target location (4 vs. 6)	Congruency*Threat + Congruency*Target location + Intensity	6472	17	$\chi^2(2) = 0.20$	0.91

TABLE 2. Step 2. Determine fixed effects – Trim down the model. Decision: choose model 6 with the interaction between congruency and target location, and congruency and threat.

Effects	***B***	**SE(B)**	χ^2	Df	*p*
Intercept	1.81	0.27	45.85	1	<0.001
Congruency	-0.46	0.18	6.51	1	0.01
Threat	-0.34	0.09	14.91		<0.001
Target location	0.16	0.28	0.30	1	0.58
Intensity	-0.93	0.17	31.33	1	<0.001
Congruency * Threat	0.24	0.13	3.66	1	0.06
Congruency * Target location	0.54	0.14	15.83	1	<0.001

TABLE 3. Step 3. Test final model.

CHAPTER 5

DOES PAIN ANTICIPATION AFFECT CROSSMODAL INTERACTIONS BETWEEN VISION AND TOUCH?[5]

ABSTRACT:

When facing bodily threats, it is crucial to localize the source of the threat as quickly as possible to be able to respond adequately. Sensory information associated with threatening events often emerges from multiple modalities on and around the body (e.g. visual and somatosensory) and can be integrated to facilitate the localization of threat, especially near the body (i.e. peripersonal space). However, it has not yet been studied whether such crossmodal interactions between visual and tactile stimuli are facilitated near a body-part that is threatened by imminent pain. We investigated this by asking healthy volunteers (N = 15) in a temporal order judgment (TOJ) task to judge which of two vibrotactile stimuli, one applied on either hand and separated by various stimulus onset intervals (SOAs), was presented first. Tactile targets were shortly preceded by visual stimuli, presented either on the same side or the opposite side of the first tactile stimulus or on oth sides, and either near or far from the hands. In addition, participants were informed that a painful electrocutaneous stimulus could be applied to one of the hands (threatened hand). We expected that participants' judgments would be shifted towards the visually cued side, especially in near space, and that this visual cueing effect would be stronger around the threatened hand. We found that judgments were indeed shifted towards the cued side in near space, but not in far space. However, the effect of bodily threat on this visual cueing effect was unclear and did not seem to facilitate visuo-tactile interactions. In conclusion, this study corroborated the existence of a crossmodal link between vision and touch in peripersonal space, but we could not draw definite conclusions about the effect of bodily threat on crossmodal interactions.

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[5] Van der Biest, L., Legrain, V., De Paepe, A.L., Crombez, G. (unpublished manuscript). Does bodily threat affect crossmodal interactions between vision and touch?

INTRODUCTION

In order to protect our body from physical harm, it is quintessential to detect and localize the source of threats as quickly as possible. Only when the source of threat is successfully localized with respect to the body, it is possible to respond adequately (Legrain, Iannetti, Plaghki, & Mouraux, 2011). However, in real life threatening events are often not unimodal in nature, but comprise information from multiple modalities (e.g. visual and somatosensory). For example, being attacked by a wasp can be associated with both visual and auditory information near the body, and also nociceptive information on the body surface. Multisensory studies have shown that the brain is able to coordinate, or even integrate, the processing of stimuli from different sensory modalities, as if they originated from the same source (Driver & Spence, 1998a; Eimer & Driver, 2001; Spence, 2010; Spence & Driver, 2004; Spence, Pavani, & Driver, 2004). Although crossmodal integration poses a challenge to the brain, which needs to integrate sensory information from different frames of reference (e.g. retinotopic for vision, somatotopic for touch), the result is a more stable and coherent representation of space, thereby facilitating the localization of potentially threatening events (Spence & Driver, 2004).

Crossmodal interactions have been demonstrated for most combinations of sensory modalities (Driver & Spence, 1998a; Eimer & Driver, 2001; Lloyd, Merat, McGlone, & Spence, 2003; Macaluso & Driver, 2001; Spence, Nicholls, Gillespie, & Driver, 1998; Spence, Pavani, & Driver, 2000). When aiming to protect the body, it might be of particular interest to process sensory events that are close to the body, where they may cause actual damage to the body (Legrain & Torta, 2015). The region of space around the body in which objects are within reach and can readily be manipulated – i.e. the peripersonal space – has been described as a defensive safety margin for incoming threats and has proven to facilitate crossmodal interactions, especially between visual and somatosensory stimuli (Làdavas, di Pellegrino, Farnè, & Zeloni, 1998; Sambo & Forster, 2009; Spence et al., 1998). For example, Spence, Nicholls, Gillespie and Driver (Spence et al., 1998) have used the orthogonal cueing paradigm to measure the effect of visual stimuli on the discrimination of tactile stimuli. They found that accuracy and reaction times were better when visual cues were presented on the same side as the tactile targets, compared to the opposite side, especially when visual cues were presented close to the body, as opposed to far. A recent study also demonstrated crossmodal interactions with vision and nociception in peripersonal space (De Paepe, Crombez, & Legrain, 2015). In this study, participants' judgments of the temporal order of pairs of nociceptive stimuli, one applied to either hand, were biased by the occurrence of a visual stimulus near one of the hands at the advantage of the nociceptive stimulus applied on that hand. Moreover, this crossmodal interaction effect was less pronounced when visual cues were presented far from the hands, in extrapersonal space. These results suggest that, similarly to tactile stimuli, the processing of nociceptive stimuli is influenced by peripersonal frames of reference that allow crossmodal interactions.

An intriguing question is whether these crossmodal interactions are facilitated near a body-part on which pain is anticipated. The effect of (pain-induced) bodily threat on attentional processes has been investigated, but mostly within one single modality (Durnez & Van Damme, 2015; Van Damme, Crombez, & Eccleston, 2004; Van Hulle, Durnez, Crombez, & Van Damme, 2015; Vanden Bulcke, Crombez, Durnez, & Van Damme, 2015). A few authors (de Haan, Smit, Van der Stigchel, & Dijkerman, 2016; Poliakoff, Miles, Li, & Blanchette, 2007; Van Damme, Gallace, Spence, Crombez, & Moseley, 2009) did observe increases in crossmodal interactions under threatening conditions, but generally used threatening pictures to induce threat. For example, a threat-related processing bias of tactile information was found toward the hand where threatening pictures were presented, especially when physical threat was implied (e.g. picture of snake intending to bite), compared to general threat (e.g. picture of a sinking ship) or compared to no threat (e.g. picture of a cow). However, threatening pictures, instead of actual pain stimuli, might be less suited to assess increases in crossmodal interactions near a specific body-part on which pain is anticipated.

Taken together, no study has investigated crossmodal interactions between visual and somatosensory stimuli when an individual is threatened by the imminence of pain. If crossmodal integration serves the function of detecting and localizing potential bodily threat, we may expect that the anticipation of pain will facilitate this integration, especially in the peripersonal space. We tested this research question by asking healthy participants which of two vibrotactile stimuli, one administered to either hand, they perceived as occurring first in a temporal order judgment (TOJ) task. Tactile stimulus pairs were shortly preceded by either a brief light flash presented one of the two sides or two flashes presented on both sides simultaneously, and either near the hands (peripersonal space) or far from the hands (extrapersonal space). In addition, participants were instructed that occasionally (i.e. 10% of the trials), the tactile stimulation pair would be replaced by a painful electrocutaneous (EC) stimulus, delivered on one hand. Participants knew in advance which of the hands would receive the EC stimuli. That way pain was anticipated in one hand, but not in the other hand. We measured to what extent the anticipation of pain shifts attention to the threatened side and facilitates the crossmodal interaction between visual and tactile stimuli at the side of space corresponding to the threatened hand (i.e. where pain is expected). When visual stimuli were bilateral, we expected a shift of attention towards the threatened hand. When visual stimuli were unilateral and close to the hands (i.e. peripersonal space), we expected a shift of attention towards the hand where the visual stimuli were presented, but we expected this effect to be stronger when that hand was threatened than when the opposite hand was threatened. When unilateral visual cues were far from the hands (extrapersonal space), we expected less effect from the location of visual stimuli and bodily threat on tactile processing.

METHOD

PARTICIPANTS

Nineteen healthy volunteers (age: *M* = 38.3, SD = 13.68, range = 23 – 60 years; 5 male; 2 left handed) participated in this experiment. Participants were randomly selected (method: random number generator) from an online volunteers database of research volunteers that were recruited through newspaper advertisements. Participants were included when they were aged between 18 and 65 years and were

Dutch-speaking. They were excluded when they reported significant sensory loss on the hands, loss of functionality of the feet, acute or chronic pain of the upper limbs, insufficiently-corrected visual impairments, current psychiatric, neurological or heart conditions, pregnancy, or intake of psychotropic medication or other drugs that affect the central nervous system. One participant reported intake of psychotropic medication at the moment of testing and was post-hoc excluded. Also, the experiment was discontinued for one participant who was not able to perform adequately on the task. As such, fifteen participants (age: M = 38.41, SD = 13.71, range = 24 – 60 years, 4 male, 2 left handed) were included in the experiment. The experiment was approved by the Ethics Committee of Ghent University. All participants provided written informed consent and received a compensation of €25.

STIMULI AND APPARATUS

Participants were seated in a dimly lit room with their hands, palms down, resting on a table (see Figure 1). The left or right foot was placed on a foot pedal on the floor that could be operated by lifting the front or the back of the pedal with the toes or heel. The distance between the index fingers was 40cm and the distance between the edge of the table (near the participant's trunk) and the index fingers was approximately 35cm. All participants had their head fixed in a chin wrest and wore headphones through which white noise (46dB) resounded.

VISUAL STIMULI

Light emitting diodes (LEDs) were used for visual stimuli. Four green LEDs were placed on the table. Two LEDs were positioned between the thumb and index finger of either hand (near visual stimuli). The two other LEDs were positioned on the same sagittal axes but at a distance of 70 cm in front of the index fingers (far visual stimuli). A red LED, serving as a fixation point, was placed in front of the participants at an equivalent distance from the four green LEDs.

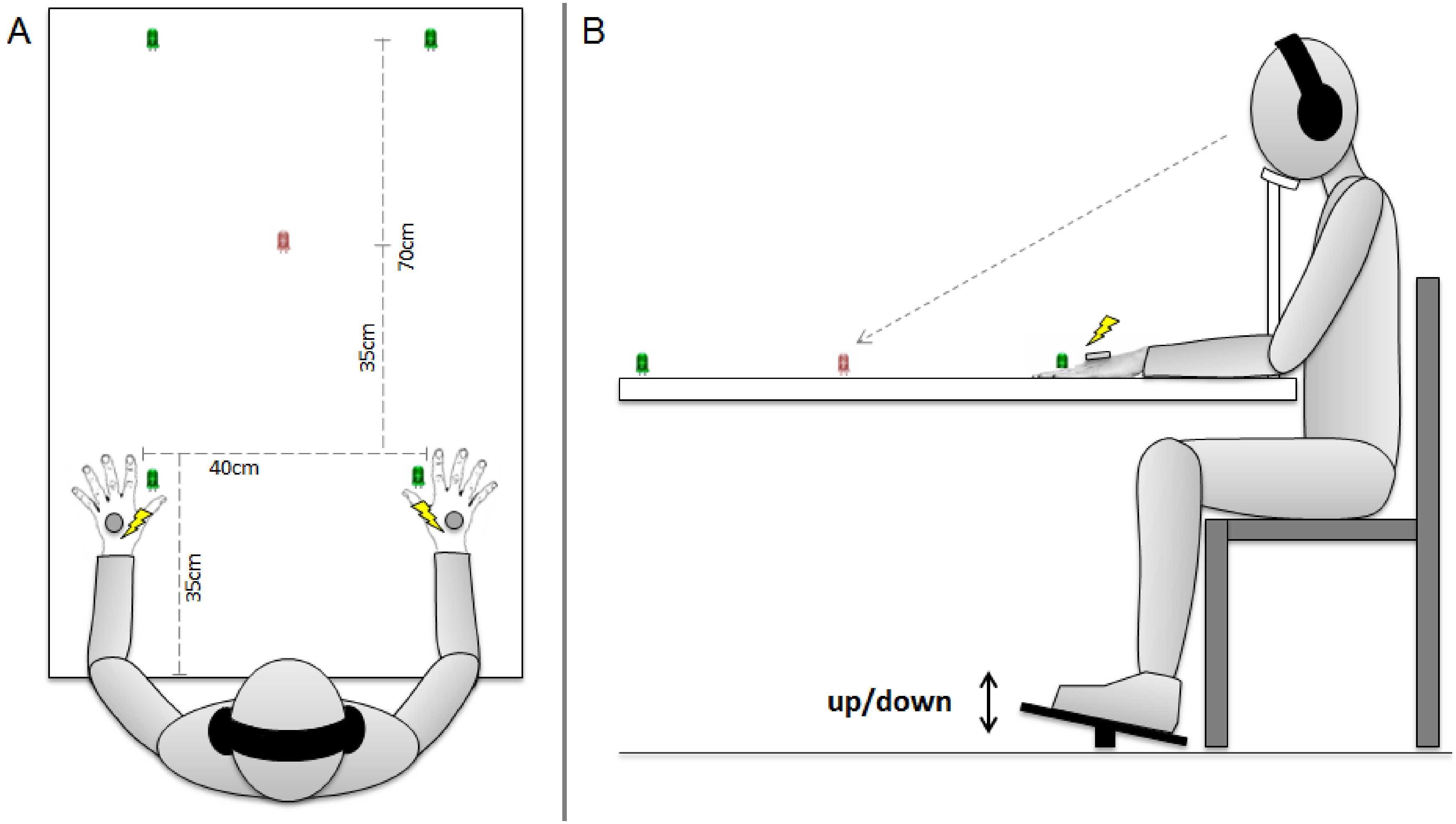

FIGURE 1. Experimental set-up of TOJ task. Panel A: top view of set-up. Panel B: side view of set-up, illustrating foot pedals under the participants' left or right foot, operated by lifting the front or back of the foot.

VIBROTACTILE STIMULI

Vibrotactile stimuli were delivered by means of two moving magnet linear actuators (C-2 TACTOR, Engineering Acoustics, Inc., Florida) placed on the third metacarpal of each hand dorsum. Vibrotactile stimuli (3.33ms, 300 Hz) were controlled by self-developed software and a controlling device that converted electrical signals into oscillating movements of the actuators against the skin. Intensity of the vibrotactile stimuli was adjusted individually and matched between the hands using a double random staircase procedure, based on the 'simple-up-down' method of Levitt (Levitt, 1971). First, 16 stimuli were administered on the left hand to be compared to a reference stimulus with maximum power (0.21 Watt) on a 5-point Likert scale ranging from 1 ("almost no sensation") to 5 ("maximum intensity"). The intensity corresponding to an average rating of 3 was selected as the stimulus intensity for the left hand, and was used as the reference stimulus for the second part of the staircase procedure. In the second part, another 16 stimuli were presented, now to the right hand, and were compared to the selected 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"). Similarly, the intensity resulting in an average rating of 3 was selected as the intensity for the right hand.

ELECTROCUTANEOUS STIMULI

Electrocutaneous (EC) stimuli were delivered by two pair of Ag-AgCl electrodes (1cm diameter) placed on the sensory territory of the superficial radial nerve of each hand, and driven by two constant current stimulators (Digitimer DS5 2000, Digitimer Ltd, UK). The electrostimulators were set at a duration of 200ms and a frequency of 50 Hz. Stimulus intensity was determined for each participant by means of a double-random staircase procedure. On each hand separately, 20 stimuli were presented (starting intensity between 0 and 1.8 mA) and self-reports were collected on a 11-point Likert scale (0 = "no pain"; 10 = "unbearable pain"). The stimulus was set at an intensity corresponding to an average rating of 7.

SELF-REPORT MEASURES

Before the start of the experiment, participants completed an anamnestic questionnaire (ad hoc developed), the Pain Grading Scale (Von Korff, Ormel, Keefe, & Dworkin, 1992), the Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995) and the trait items of the State-Trait Anxiety Inventory (STAI; Spielberger, 1987). At the end of the experiment, a series of self-report items assessed *i)* the perceived intensity of the visual, vibrotactile and EC stimuli (Likert scale from 0 "not intense at all" to 10 "very intense") and assessed to what extent participants *ii)* directed their attention towards each of these types of stimuli; *iii)* felt threatened by the EC stimuli; *iv)* believed the instruction that EC stimuli would only be administered unilaterally; *v)* believed the instruction that EC stimuli would only be presented to the hand (left/right) that was instructed; *vi)* strategically used the near and/or far visual cues to predict the location of the tactile stimuli; *vii)* made an effort to complete the task; *viii)* were concentrated during the task; *ix)* experienced fear/tension during the task and *x)* found the task meaningful (i.e. not having to guess; all measured on a Likert scale from 0 "not at all" to 10 "very much"). Responses on the PCS and STAI were collected for meta-analytic purposes and will therefore not be reported here.

PROCEDURE

After completing the questionnaires, participants were seated comfortably at the table and received instructions about the staircase procedures. The experimenter attached the actuators and electrodes to the hands and checked the visibility of the LEDs. Headphones were turned on and the staircase procedure for the vibrotactile stimuli initiated. Participants were asked to rate the intensity of a series of vibrotactile stimuli on the left hand to a preceding reference stimulus of maximal intensity, also on the left hand, on a 5-point Likert scale from 1 ("almost no sensation") to 5 ("maximal sensation"). After that, they rated the intensity of a series of vibrotactile stimuli on the right hand, compared to a reference stimulus of moderate intensity 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"). Responses were inserted manually by the experimenter on a keyboard. Following this, the staircase procedure for the EC stimuli started in which participants were asked to rate the pain intensity of a series of EC stimuli on either hand on a Likert scale from 0 ("no pain") to 10 ("unbearable pain"). After finishing the staircase procedures, headphones were temporarily removed.

Before the start of the temporal order judgment (TOJ) task, participants received instructions about the task and were asked to keep their gaze on the red fixation LED in front of them, to place their head on the chin wrest and to keep their hands still throughout the experiment. After these instructions, the participants' left or right foot was placed on the foot pedal and headphones were turned back on. During the TOJ task, participants were asked to judge the temporal order of two tactile stimuli, one presented to either hand. Each trial started with the illumination of the red fixation LED. After a 1000ms delay, either one (unilateral visual cues) or two (bilateral visual cues) green LEDs were illuminated (duration 20ms) near the hands (near visual cues) or far from the hands (far visual cues). This was immediately followed by a pair of vibrotactile stimuli presented to either hand. Stimulus onset asynchronies (SOA) between the two vibrotactile stimuli were ±200, ±90, ±55, ±30 or ±10ms (negative values indicating that the left hand was stimulated first) and were presented randomly and equiprobably (Gallace & Spence, 2005). Participants were instructed to respond on which hand they felt the tactile stimulus first (left vs. right) by lifting the front or the back of their foot on the foot pedal (which foot and which lifting movement to make was counterbalanced). That way, response mapping was orthogonal to stimulus presentation, minimizing the possibility of a response bias (Filbrich, Torta, Vanderclausen, Azañón, & Legrain, 2016; Spence & Driver, 2004). At the beginning of each block, participants were informed that in some trials the vibrotactile stimulus might be replaced by a painful stimulus on their left or right hand (alternated between blocks). In those cases, they were asked to respond on which hand they felt the painful EC stimulus. Participants were always unaware of the number of EC stimuli that would be delivered.

Participants first completed three practice blocks to get familiar with the task and with the response mapping (foot pedal). In practice block 1 (16 trials), participants practiced response mapping by localizing single tactile stimuli on the hands. In practice block 2 (14 trials), participants were instructed to make temporal order judgments of pairs of vibrotactile stimuli, separated only by the three largest SOA's (±200, ±90, and ±55ms). Tactile stimuli were preceded by far bilateral visual cues only. Participants were also informed that painful stimuli (EC stimuli) on the left/right hand (counterbalanced) might be administered on some of the trials. This was the case for 2 trials. Practice block 3 (26 trials) was designed to further train participants in making temporal order judgments, but now preceded by near unilateral visual cues. Again, two EC stimuli were administered, but now to the opposite hand as in practice block 2. The practice blocks were repeated until a performance of 75% (correct responses) on the largest SOA (±200ms) was achieved.

The experimental design is illustrated in Figure 2. In each of the four experimental blocks, participants judged the temporal order of 120 pairs of tactile stimuli on the hands. The laterality of the visual cues (unilateral left/right and bilateral) and the different SOA's were divided randomly and equiprobably within each block. In an additional 12 trials per block, EC stimuli were administered to the left or the right hand (which hand was alternated between blocks). The distance of the visual cues was near in two blocks and far in two blocks (order randomized) and crossed with the location of threat (i.e. left/right).

TOJ MEASURES

The calculations of the TOJ measures were based on the procedure of Spence, Shore and Klein (Spence, Shore, & Klein, 2001). For trials with unilateral visual cues, the proportion of trials on which participants perceived the tactile stimulus on the *cued* side first was calculated for each participant, for each SOA, for each distance of the visual cues (near vs. far) and for each location of the threat (ipsi- vs. contralateral to the visual cues). For trials in which visual cues were presented bilaterally, the proportion of trials on which participants perceived the tactile stimulus on the *threatened* side first was calculated for each participant, each SOA, and for each distance of the visual cues (near vs. far).

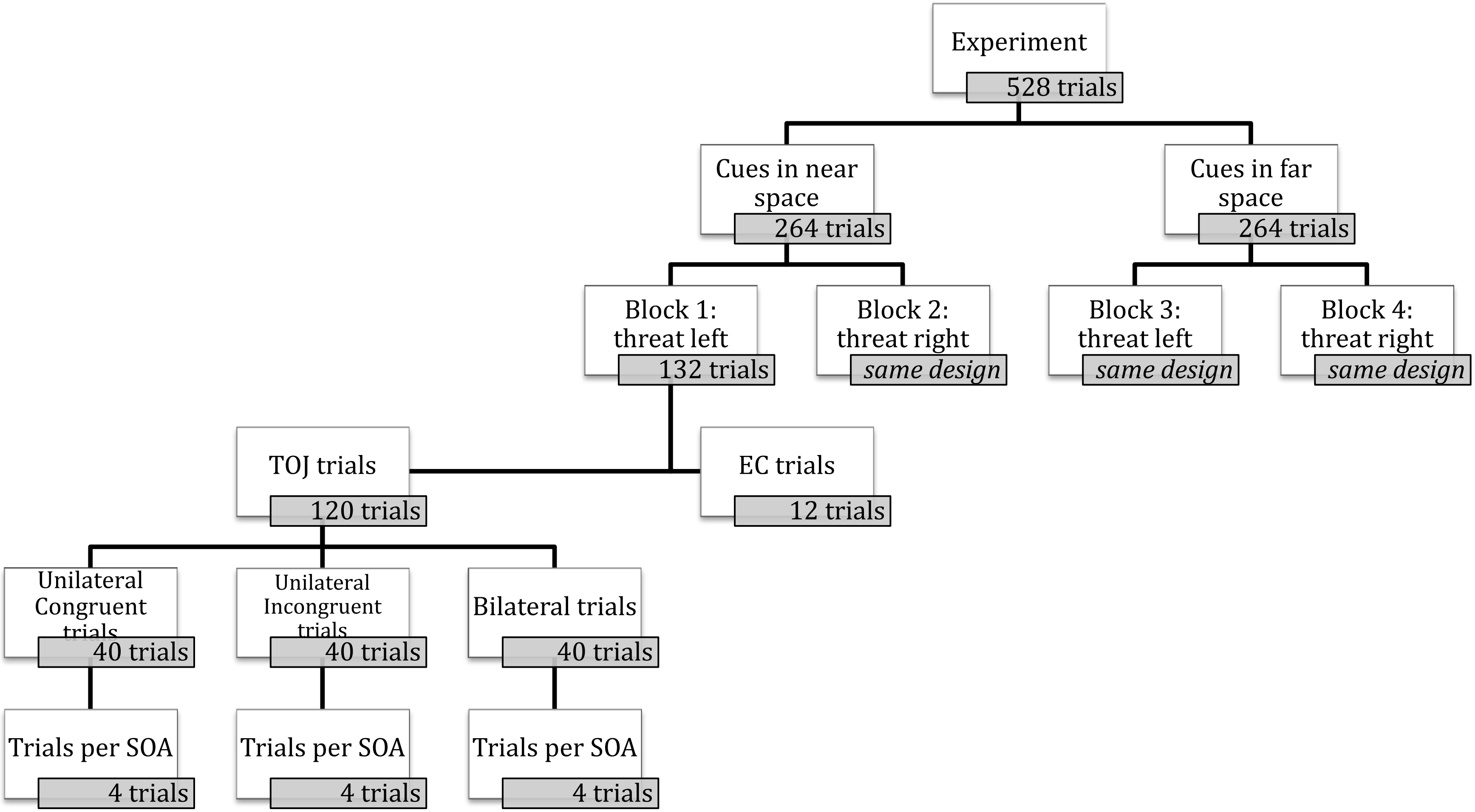

FIGURE 2. Experimental design of the TOJ experiment. Example of experimental design in which the distance was near in the first two blocks and far in the last two blocks (order was randomized). The location of threat (left/right) was always alternated between blocks. Trials were identically divided within the four experimental blocks.

A sigmoid function was fitted to these proportions and a standardized cumulative normal distribution (probits) was used to convert the proportion of left hand/right hand first responses into a z-score. The best-fitting straight line was computed for each participant and for each of the conditions. The derived slope and intercept were used to calculate 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 (left hand first and right hand first) equally often. This is equivalent to the SOA at which the participants perceive the two stimuli as occurring at the same time (0.5 proportion of left hand/right hand first responses) (Spence et al., 2001). To calculate the PSS, the opposite of the intercept is divided by the slope, both derived from the best-fitting straight line. To simplify the interpretation of the PSS values in the unilateral condition, the sign was reversed for the trials in which the visual cue was on the right side of space so that in the analyses the cued side was always the left side. As such, the PSS value indicates how much time (milliseconds) the stimulus on the *uncued* side needs to be presented before or after the stimulus on the *cued* side, to be perceived as simultaneously presented. In this case, a positive PSS reflects the prioritization of tactile stimuli on the cued side. Similarly for the analysis of threat in the bilateral condition, the sign of the PSS was reversed for the trials in which the threat was on the right side, resulting in a PSS that reflects the prioritization of tactile stimuli on the threatened side.

The JND indicates the time interval (milliseconds) between tactile stimuli on the left and the right hand needed to achieve 75% correct performance, and provides a standardized measure of the sensitivity of participants' temporal perception. To calculate the JND, 0.675 is divided by the slope of the best-fitting straight line and corresponds to the value obtained by subtracting the SOA at which the best-fitting straight line crosses the 0.75 point from the SOA at which that same line crosses the 0.25 point, and dividing it by 2 (Spence et al., 2001).

ANALYSES

Participants were excluded from the analysis if one of their PSS values was greater/smaller than twice the largest SOA (i.e. ±400ms), or if their performance (% correct responses) for the largest SOA (i.e. ±200ms) in one of the conditions was below 75%. EC trials were not included in the analyses. We tested whether participants prioritized tactile stimuli *i)* on the *cued* side; *ii)* on the *threatened* side; and *iii)* and on the *cued* side, but depending on whether the threat was made on the ipsilateral versus the contralateral side, by analyzing the respective PSS values. For each of these research questions, we used one-sample *t*-tests to test whether the PSS significantly differed from 0ms (De Paepe, Crombez, Spence, & Legrain, 2014; Moseley, Gallace, & Spence, 2009) and ANOVAs for repeated measures to compare the PSS across conditions.

For analyzing the prioritization of tactile stimuli on the *cued* side (i.e. in unilateral trials), we used one-sample *t*-tests to investigate the significance of PSS shifts towards the *cued* side. An ANOVA with *Distance* of the visual cues (near vs. far) as *within-subject factor* was performed to evaluate the effect of visual cueing in near and far space. This analysis did not take threat laterality into account, and may therefore provide an indication of the basic visual cueing effect.

Analyzing the prioritization of tactile stimuli on the *threatened* side, we only included bilateral trials. By excluding unilateral trials, we investigated the effect of threat, regardless of the laterality of visual cues. One-sample *t*-tests were used to investigate the significance of PSS shifts towards the *threatened* side. An ANOVA with *Distance* (close vs. far) as within-subject factor of the visual cues was done to investigate the effect of threat when cues were near and far.

For analyzing the prioritization of tactile stimuli on the *cued* side (i.e. in unilateral trials), but depending on the laterality of threat (ipsi- vs. contralateral to the visual cues), we used one-sample *t*-tests to investigate the significance of PSS shifts towards the *cued* side when threat was ipsilateral or contralateral. An ANOVA with *Threat Laterality* (ipsilateral vs. contralateral) and *Distance* (near vs. far) as within-subject factors was conducted to investigate the effect of threat on crossmodal interactions. If threat facilitates crossmodal interactions in peripersonal space, we expect a significant two-way interaction between *Threat Laterality* and *Distance*, whereby the PSS is higher when threat is ipsilateral to visual cues, especially when visual cues are presented near the hands.

All ANOVA's were performed on the PSS and JND values. Significance levels were set at $p < 0.05$.

RESULTS

PARTICIPANTS

Three participants were excluded, two because of unsatisfactory performance (<75%) on the TOJ task and one due to a PSS exceeding ±400. Fifteen participants (age: $M = 38.47$, SD = 13.71, range = 24 – 60 years; 4 male; 2 left handed) remained included for further analysis.

STAIRCASES

The intensity of the tactile stimuli did not differ between the left and the right hand (left hand: $M = 0.108$, SD = 0.029; right hand: $M = 0.110$, SD = 0.047; $F(1,14) = 0.046$, $p = 0.834$). The intensity of the EC stimuli was higher for the right hand ($M = 0.098$, SD = 0.054) than for the left hand ($M = 0.071$, SD = 0.037; $F(1,14) = 18.85$, $p < 0.01$). This difference in intensity of the EC stimuli was not determined by handedness of the participants ($F(1,12) = 0.389$, $p = 0.544$).

SELF-REPORT MEASURES

Participants reported high effort ($M = 8.47$, SD = 1.73) and concentration ($M = 7.87$, SD = 1.19) and low fear/tension ($M = 1.73$, SD = 1.79) during the TOJ task. The amount of attention directed to the tactile and to the EC stimuli was very similar (tactile stimuli: $M = 6.60$, SD = 2.85; EC stimuli: $M = 6.73$, SD = 2.63) but the intensity was rated higher for the painful stimuli than for the tactile stimuli (EC stimuli: M = 5.87, SD = 2.00; tactile stimuli: M = 3.53, SD = 2.53). Participants felt only mildly threatened by the EC stimuli (M = 2.87, SD = 2.72), did not expect to receive EC stimuli to the opposite hand than instructed (M = 1.93, SD = 2.46) and trusted the instruction that EC stimuli would only be administered unilaterally (M = 9.40, SD = 1.06). Visual stimuli received moderate attention (M = 3.87, SD = 2.62), were rated moderate in intensity (M = 4.47, SD = 2.80) and were not strategically used to predict the location of the tactile stimuli (using close cues to predict TOJ: M = 1.80, SD = 1.66: using far cues to predict TOJ: M = 1.00, SD = 1.60). Participants rated the task as very meaningful (i.e. not having to guess; M = 8.00, SD = 1.25).

TOJ MEASURES

Analysis of the prioritization of tactile stimuli on the *cued* side yielded the following results (see Figure 3). One-sample t-tests showed that the PSS was significantly positive when visual cues were presented near the hands (M = 28.25, SD = 35.75, $t(14)$ = 3.06, $p < 0.01$, CI = [8.45:48.05]), meaning that there was a shift towards the cued side in near space. More specifically, it shows that tactile stimuli on the *uncued* side needed to be presented about 28ms earlier than the stimuli on the *cued* side to be perceived as simultaneous. When cues were presented far from the hands, the PSS did not differ from zero (M = 4.53, SD = 19.66, $t(14)$ = 0.89, p = 0.387, CI = [-6.35:15.42]). The ANOVA comparing attention shifts towards the *cued* side between each distance (near vs. far) of the visual cues revealed a marginally significant main effect of *Distance* ($F(1,14)$ = 3.14, p = 0.098; Cohen's d = 0.50, CI = [-0.04:1.03]), showing a more positive PSS when visual cues were near the hands.

Analysis of the prioritization of tactile stimuli on the *threatened* side revealed the following results (see Figure 4). A significantly negative PSS appeared when cues were presented near the hands (M = -23.38, SD = 25.40, $t(14)$ = -3.56, $p < 0.01$, CI = [-37.44:-9.31]), reflecting a shift away from the threatened side. The PSS did not differ from zero when cues were presented far from the hands (M = -10.05, SD = 59.54, $t(14)$ = -0.65, p = 0.524, CI = [-43.02:22.92]). The Repeated Measures ANOVA comparing attention shifts

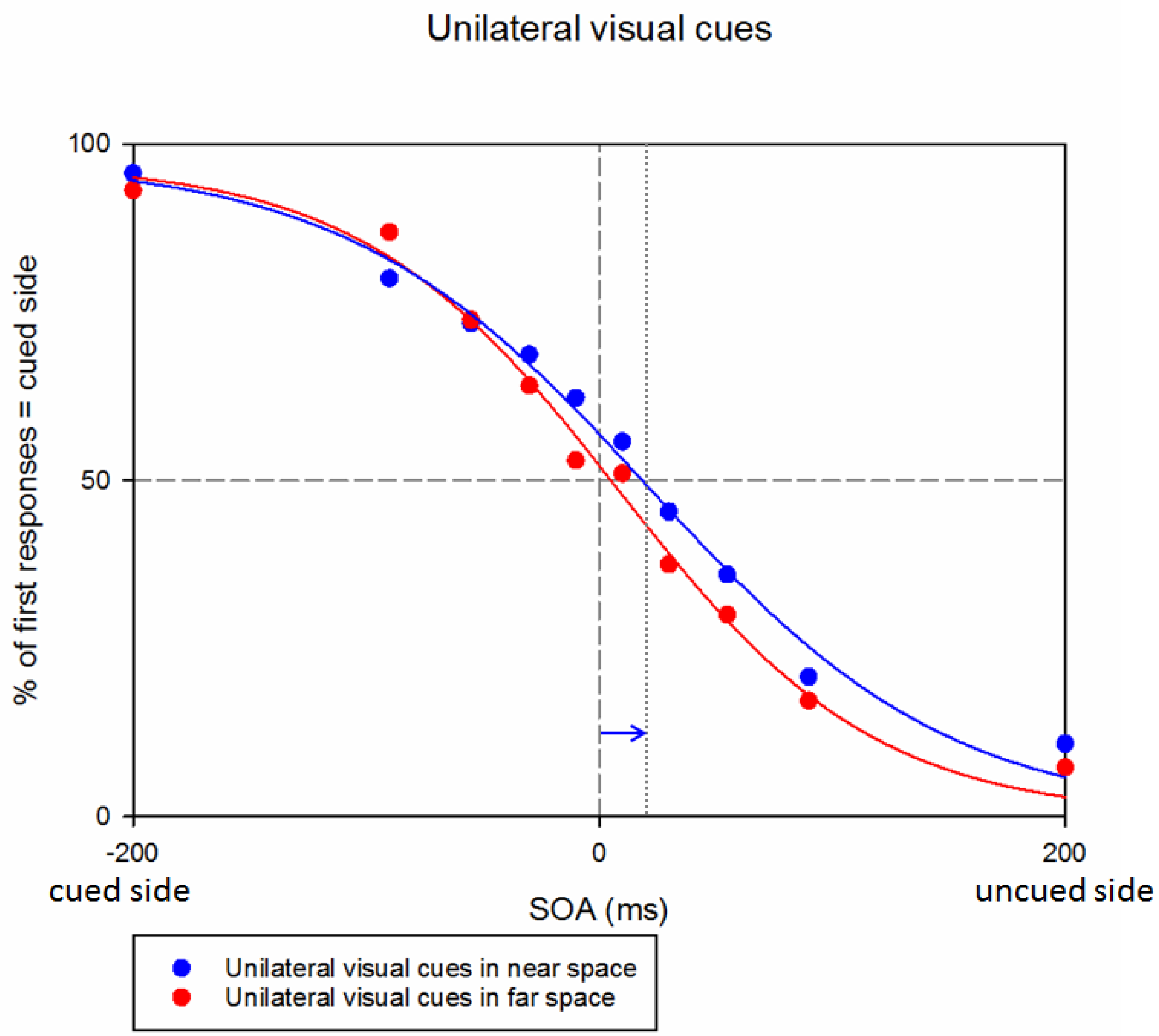

FIGURE 3. Sigmoid plot, illustrating PSS shifts towards cued or uncued side. The figure illustrates the fitted curves from the cumulative data of the 15 participants included in this study. The *x*-axis represents the SOAs between each pair of tactile stimuli presented to the hands. As the aim was to evaluate the effect of unilateral visual cues (left or right) on the TOJ for tactile stimuli, the responses were re-coded in a way that negative values on the left side of the *x*-axis indicate that the cued hand was stimulated first, whereas positive values indicate that the uncued hand was stimulated first. The *y*-axis shows the mean proportion of responses indicating that the cued hand was perceived as having been stimulated first. The blue arrow indicates that the PSS was significantly shifted towards the cued side when cues were presented near the hands.

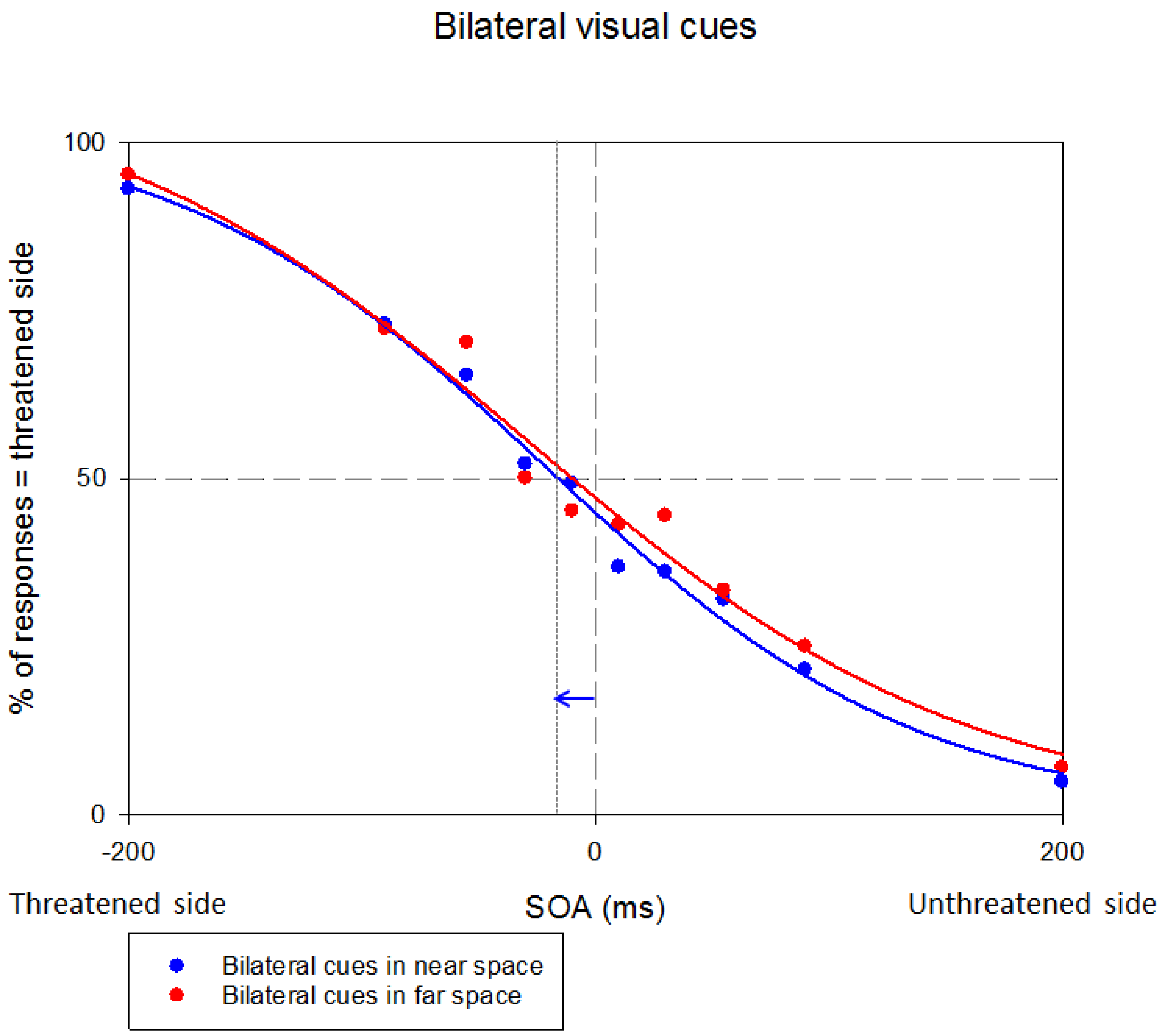

FIGURE 4. Sigmoid plot, illustrating PSS shifts towards threatened or unthreatened side. The figure illustrates the fitted curves from the cumulative data of the 15 participants included in this study. The *x*-axis represents the SOAs between each pair of tactile stimuli presented to the hands. As the aim was to evaluate the effect of threat (left or right) in bilateral trials on the TOJ for tactile stimuli, the responses were re-coded in a way that negative values on the left side of the *x*-axis indicate that the threatened hand was stimulated first, whereas positive values indicate that the unthreatened hand was stimulated first. The *y*-axis shows the mean proportion of responses indicating that the threatened hand was perceived as having been stimulated first. The blue arrow indicates that the PSS was significantly shifted away from the threatened side when bilateral cues were presented near the hands.

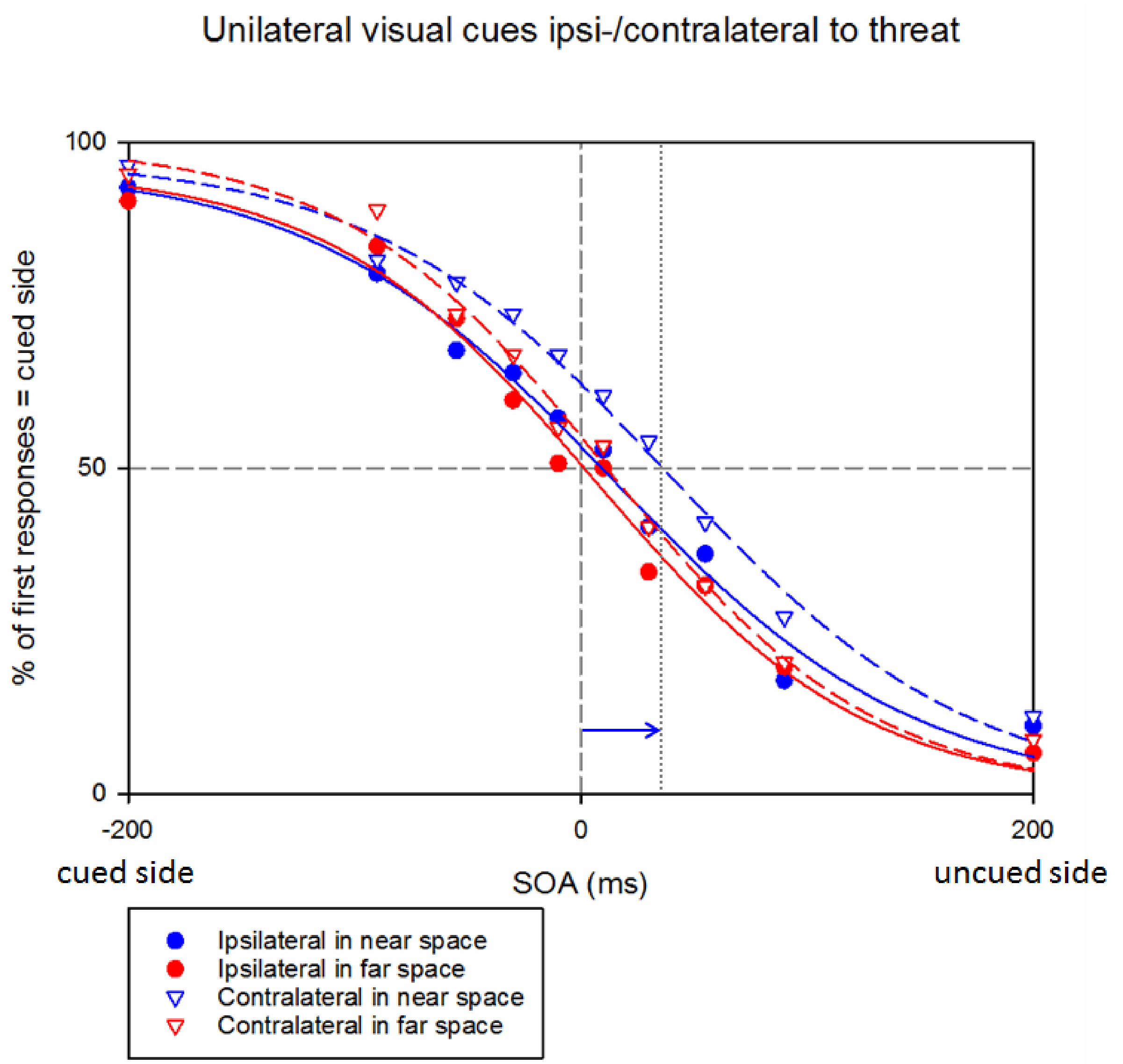

FIGURE 5. Sigmoid plot, illustrating PSS shifts towards cued or uncued side, depending on threat laterality. The figure illustrates the fitted curves from the cumulative data of the 15 participants included in this study. The *x*-axis represents the SOAs between each pair of tactile stimuli presented to the hands. As the aim was to evaluate the effect of unilateral visual cues (ipsilateral vs. contralateral to threat) on the TOJ for tactile stimuli, the responses were re-coded in a way that negative values on the left side of the *x*-axis indicate that the cued hand was stimulated first, whereas positive values indicate that the uncued hand was stimulated first. The *y*-axis shows the mean proportion of responses indicating that the cued hand was perceived as having been stimulated first. Solid lines represent trials in which visual cues and threat were presented on the same side (ipsilateral), dotted lines represent trials in which they were presented on opposite sides (contralateral). The blue arrow indicates that the PSS was significantly shifted towards the cued side when threat was contralateral and when cues were presented near the hands.

towards the *threatened* side between each distance (near vs. far) of the visual cues, however, revealed no main effect of *Distance* ($F(1,14) = 0.70$, $p = 0.416$, Cohen's $d = -0.22$, CI = [-0.73:0.29]).

Analysis of the prioritization of tactile stimuli on the *cued* side, depending on the laterality of threat (ipsi- vs. contralateral to the visual cues) yielded the following results (see Figure 5). One-sample *t*-tests revealed a highly significant positive PSS when threat was contralateral to the cues, but only when visual cues were presented in near space ($M = 42.15$, SD = 27.33, $t(14) = 5.97$, $p < 0.0001$, CI = [27.02:57.28]). More specifically, the tactile stimulus on the *uncued/threatened* side needed to be presented about 42ms earlier than the stimulus on the *cued/unthreatened* side to be perceived as simultaneous. When visual cues were presented far ($M = 6.92$, SD = 73.99, CI = [-34.05:47.89]) or when threat was ipsilateral to the visual cues (ipsilateral close: $M = 15.66$, SD = 77.99, CI = [-27.53:58.85], ipsilateral far: $M = 5.05$, SD = 32.53, CI = [-12.96:23.06]), PSS values did not differ from zero (not significant). The Repeated Measures ANOVA comparing attention shifts towards the *cued* side, depending on the *Threat Laterality* (ipsilateral vs. contralateral to the visual cues) and the *Distance* (near vs. far) of the visual cues showed no significant results.

Analysis of the JND revealed no differences between any of the conditions (not significant).

DISCUSSION

The aim of this study was to investigate the effect of pain-induced bodily threat on crossmodal interactions in peripersonal space. We expected an effect of spatially uninformative visual cues on tactile processing when visual cues were presented near the hands but not when they were presented far from the hands. Importantly, we expected this visuo-tactile interaction to be stronger when the cued location was threatened by the anticipation of painful stimuli on the hands.

Overall, our study replicated some findings reported in previous studies. The results from this study demonstrated an effect of visual cueing on tactile temporal order judgments in peripersonal space, as evidenced by a significantly positive PSS when visual cues were presented in near space, as opposed to far space. These results are in line with many studies demonstrating visuo-tactile interactions in peripersonal space (Driver & Spence, 1998b; Spence & Driver, 1997; Van der Biest, Legrain, De Paepe, & Crombez, 2016). The effect of bodily threat on attention shifts was less clear. When visual cues were bilateral – and thus could not cause shifts in tactile processing – there was no attentional bias towards the threatened hand, in contrast to what we expected. A bias *away* from the threatened side appeared when bilateral cues were near the hands, but not when they were far from the hands. Furthermore, when visual cues were unilateral, the laterality of the threat (ipsilateral vs. contralateral to the visual cues) did not affect the visuo-tactile interaction. However, a relatively large bias towards the cued side was found for nearby visual cues, but only when threat was contralateral to the cues. In sum, these results suggest that there was an attentional bias *away* from the threatened hand, rather than a bias towards threat, which is in contradiction to earlier findings of pain/threat drawing attention to the painful/threatened location (Van Damme, Crombez, & Lorenz, 2007; Van Damme et al., 2009; Vanden Bulcke, Van Damme, Durnez, & Crombez, 2013).

Despite the fact that attention seemed biased away from threat, the effect of threat was not predominant. There are some methodological aspects that might explain this. First, there is the possibility that the intensity of the electrocutaneous (EC) stimuli used in this study was too low to induce bodily threat. This assumption is supported by the self-report measures: even though participants rated the intensity of the EC stimuli as moderately high (M = 5.87, SD = 2.00), they also reported feeling only mildly threatened by them (M = 2.87, SD = 2.72). This is consistent with a study (Van Damme et al., 2007) reporting a bias in visual attention towards the pain location, only when the pain was perceived as threatening. Second, the relatively small sample size might have caused a lack of power in the analyses. For example, the difference in visual cueing effects between near and far space was only marginally significant (p = 0.098), even though the effect size was 0.50 (moderate effect).

On the other hand, it could be that the manipulation of bodily threat failed because EC stimuli were not sufficiently attended. Although participants reported attending the EC stimuli to a fairly large extent (*M* = 6.73, SD = 2.63), this does not necessarily imply that the threatened location was attended *during non-EC trials* – i.e. the trials that were included in the analyses. Also, the fact that bodily threat was continuously present throughout the TOJ task and not, for example, signaled on a trial-to-trial basis by means of a cue (Vanden Bulcke et al., 2013), could have diminished attention towards the threat location. A lack of attention for EC stimuli/bodily threat could have also been caused by the visual cues capturing the attention to such a large extent that they overruled any effects of (task-irrelevant) bodily threat, for example, due to limitations in working memory capacity (Legrain et al., 2009; Legrain, Crombez, & Mouraux, 2011). In this respect, attentional biases towards pain-induced threat, as reported in previous studies, are not automatic or hard-wired but depend on the context (e.g. ongoing cognitive task). In some cases, attention can even be biased towards the side of space, opposite to pain or threat. For example, it was observed that patients with Complex Regional Pain Syndrome tend to prioritize stimuli on the non-pathological hand, to the detriment of stimuli on the pathological hand (Moseley et al., 2009). Although one should be careful in comparing results of chronic pain populations with those of healthy participants, these findings at least illustrate that attention is not automatically directed towards the location of pain or threat. This was also supported by a recent meta-analysis and theoretical framework on pain-related attentional biases (Todd et al., 2015). The authors propose that, whereas the initial processing of threatening stimuli is characterized by increased vigilance, avoidance of threatening stimuli may occur at later stages, for example when stimuli are no longer threatening or, conversely, when threat levels are very high (see also Baum, Schneider, Keogh, & Lautenbacher, 2013; Priebe, Messingschlager, & Lautenbacher, 2015). As participants in our study were only mildly threatened by the EC stimuli, it could be that they initially prioritized stimuli on the threatened body-part, but then learned to avoid these stimuli, as they were no longer threatening. Unfortunately, the design of this experiment did not permit us to test this hypothesis.

Taken together, this study was able to replicate earlier findings on the crossmodal interaction between visual and somatosensory (tactile) stimuli in peripersonal space. However, the effect of pain anticipation on these crossmodal interactions was unclear. Bodily threat did not seem to induce changes in tactile processing, nor did it enhance crossmodal interactions near the threatened body-part. Some analyses even suggested a bias in the opposite direction of the threat. Clearly, future studies are needed that further investigate the effect of bodily threat on crossmodal effects and that aim to reconcile the findings from this study with the literature on threat- and pain-related attentional biases.

ACKNOWLEDGEMENTS

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CONFLICTS OF INTEREST

The authors have no conflicts of interest related to the present study.

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PART III

CHAPTER 6

AN INVESTIGATION OF PERCEPTUAL BIASES IN COMPLEX REGIONAL PAIN SYNDROME[6]

ABSTRACT:

Complex regional pain syndrome (CRPS) has been the topic of interest in many studies. CRPS patients do not only chronically suffer from sensory, motor and vegetative symptoms, but may also display cognitive deficits such as impairments in mentally representing the pathological limb or in detecting or localizing stimuli on the affected limb. In a TOJ task by Moseley et al. (2009), it was observed that CRPS patients tend to bias the perception of tactile stimulation *away* from the pathological limb. Interestingly, this bias was reversed when CRPS patients were asked to cross their arms, implying that this bias is embedded in a complex representation of the body that takes into account the position of body-parts. Latter studies have not always corroborated these findings on perceptual biases in CRPS or even reported biases in the opposite direction (i.e. *towards* the pathological limb). Besides conflicting evidence on perceptual deficits in CRPS patients, it is unclear whether these features are CRPS-specific or generalize to other chronic pain populations. Therefore, the aim of this study was to replicate the study of Moseley et al. (2009) and to extend it by comparing perceptual biases in a CRPS group with two non-CRPS pain control groups (i.e. chronic unilateral wrist and shoulder pain patients). In a temporal order judgment (TOJ) task, participants reported which of two tactile stimuli, one applied to either hand at various intervals, was perceived as occurring first. TOJs were made, either with the arms in a normal (uncrossed) position, or with the arms crossed over the body midline. The point of subjective simultaneity (PSS) was calculated to assess perceptual biases away from/towards the painful limb. A perceptual bias *away* from the pathological limb was expected in CRPS patients and was expected to reverse when arms were crossed. In the pain control groups, a perceptual bias *towards* the pathological limb was expected. Analysis of the PSS values revealed no consistent perceptual biases in either of the patient groups and in either of the conditions (crossed/uncrossed). Individual differences were large and might, at least partly, be explained by other variables, such as pain duration, pain intensity and temperature differences between the pathological and non-pathological hand. Further research is needed that addresses the effect of individual variables, includes larger patient samples and/or adopts a single-case approach.

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

INTRODUCTION

Complex regional pain syndrome (CRPS) is a chronic systemic disease associating sensory, motor and vegetative symptoms such as pain, temperature change, skin color change, swelling, and dystonia affecting one limb, and resulting generally from minor causes such a mild trauma of that limb (Marinus et al., 2011). CRPS is generally considered a disorder of the central nervous system, although some authors also attribute a primary role to peripheral inflammatory and sympathetic factors in the pathophysiology. Two types of CRPS are distinguished, based on the absence (CRPS type I) or presence (CRPS type II) of identifiable peripheral nerve injury (Bruehl et al., 1999). CRPS is characterized by both structural and functional changes in the cortical brain (Juottonen et al., 2002; Krause, Förderreuther, & Straube, 2006; Maihöfner et al., 2007; Maihöfner, Forster, Birklein, Neundörfer, & Handwerker, 2005; Maihöfner, Handwerker, Neundörfer, & Birklein, 2003, 2004; Pleger et al., 2005, 2014). It has been suggested that these cortical changes might be associated with cognitive dysfunctions affecting the representation and the perception of the body (Legrain, Bultitude, De Paepe, & Rossetti, 2012). At a first glance, these cognitive dysfunctions have been qualified as neglect-like symptoms as they are similar to some impairments observed in hemispatial neglect consecutive to stroke (e.g. Hasselbach & Butter, 1997). CRPS patients typically report perceiving the affected limb as disconnected from their body, foreign or even dead (Frettlöh, Hüppe, & Maier, 2006; Galer & Jensen, 1999). Also, delays in movement initiation, smaller and less frequent movements (hypokinesia), slowness of movements (bradykinesia) and a need for conscious effort to move the affected limb have been observed in CRPS patients (Frettlöh et al., 2006; Galer, Butler, & Jensen, 1995; J. S. Lewis, Kersten, McCabe, McPherson, & Blake, 2007). Difficulties in mentally representing the affected limb have been reported as well. For example, it was shown that CRPS patients have difficulties and/or are delayed in recognizing the affected limb (Moseley, 2004) and in estimating its size (Moseley, 2005), orientation (Schwoebel, Friedman, Duda, & Coslett, 2001) and position (J. S. Lewis et al., 2010). In addition, deficits in localizing (Förderreuther, Sailer, & Straube, 2004) and detecting (Moseley, Gallace, & Spence, 2009) stimuli on the CRPS affected limb have been documented.

However, the comparison to the symptomatology of hemispatial neglect is still a matter of debate, as no clear deficit has been observed for CRPS patients when tested with classic procedures normally used to investigate neglect symptoms in post-stroke populations (Förderreuther et al., 2004; Kolb, Lang, Seifert, & Maihöfner, 2012). Nevertheless, it should be noted that these classic tests generally only assess visuospatial abilities. Regarding the ability of CRPS patients to process and perceive somatosensory stimuli, some signs of mislocalization problems of tactile stimulation have been reported such as referred sensations and synchiria (i.e. stimulation on one hand evoking sensations in both hands) (Acerra & Moseley, 2005; Maihöfner, Handwerker, & Birklein, 2006; McCabe, Haigh, Halligan, & Blake, 2003). Using a temporal order judgment (TOJ) task, in which participants have to judge which of two tactile stimuli applied to either hands was perceived as being delivered first, Moseley et al. (2009) have shown that CRPS patients tend to bias the perception of tactile stimulation to the detriment of the stimulus applied on the pathological limb and at the advantage of the stimulus applied on the opposite limb. Surprisingly, this was only observed when the patients' arms were in a normal uncrossed posture. When patients were asked to cross their arms across their body midsagittal plane, their judgments were now reversed, that is, the perception of the tactile stimuli was now biased at advantage of the stimulus applied on the pathological limb and to the detriment of the stimulus applied to the healthy limb. Finally, recent experiments from the same team suggest that those deficits are limited to somatosensory stimuli, as similar tasks performed using auditory stimuli did not reveal any difficulties in CRPS (Reid et al., 2016). The fact that the direction of the somatosensory perceptual bias is depending on the patients' body posture indicates that the perceptual difficulties of CRPS patients outlined in those experiments are not accounted by deficits at the peripheral coding and the spinal transmission of somatosensory inputs (Schwenkreis, Maier, & Tegenthoff, 2009), but rather involve higher order cortical mechanisms (Janig & Baron, 2002). The results also suggest that these perceptual difficulties of tactile stimuli are not anchored to the affected limb (arm-based), but to the region of space where it normally resides (space-based). This implies that CRPS would affect complex representations of the body that are not purely somatotopically organized but also spatiotopically organized by integrating various sources of information such as proprioception (Legrain & Torta, 2015).

Yet, conflicting results have been published on several aspects of cognitive symptoms in CRPS patients. For example, some studies (Sumitani, Rossetti, et al., 2007; Sumitani, Shibata, et al., 2007; Uematsu et al., 2009) have established that the direction of perceptual biases in CRPS can be the opposite of what was already observed in previous studies. Sumitani et al. (2007) showed that perception in a visual subjective body midline judgment task was biased *towards* the CRPS affected hand. In these tasks, a visual dot was flashed in front of the patients and moved horizontally. Patients were asked to stop the dot when it was positioned on the sagittal plane of their body midline. The shift of body midline judgments was observed only when the task was performed in the dark, but not in the light, suggesting that the impaired spatial reference frame in CRPS is egocentric, as opposed to allocentric (i.e. dependent of other stimuli or objects in the visual field) in nature. In addition, these deficits were reduced following nerve block by a lidocaine injection (Sumitani, Shibata, et al., 2007). Conversely to the studies reviewed in the previous paragraph, the latter studies suggest instead that CRPS patients are characterized by perceptual deficits *toward* the side of space corresponding to the pathological limb, resulting probably from excessive information coming from the affected limb, a hypothesis that sharply contrasts with the original hypothesis of neglect of the CRPS limb.

Besides these inconsistent findings, a largely unexplored question is whether these features are specific for CRPS or can also be found in other chronic pain syndromes. For example, Frettlöh et al. (2006) observed that CRPS patients reported significantly more disownership feelings and underuse of their painful limb as compared to patients with chronic pain syndromes of other origins, whereas Kolb et al. (2012) did not notice any difference between CRPS and non-CRPS patients. But it should be noted that in this latter study, CRPS and non-CRPS patients did not reveal any perceptual bias on the tasks testing classic visuospatial abilities. Uematsu et al. (2009) observed shifts of visual subjective body midline judgments in CRPS patients but not in patients post-herpetic neuropathic pain. The absence of clear consensus leaves open the question about the specificity of the cognitive biases observed in CRPS. Based on the current literature, additional studies are indeed needed to further investigate the mechanisms of cognitive symptoms in CRPS and that determine its specificity by systematically comparing CRPS patients and pain controls within the same experimental design.

The aim of the current study was to replicate the findings of Moseley et al. (2009) on space-based perceptual biases in upper limb CRPS patients and to extend these by comparing a CRPS group with two non-CRPS pain control groups. A group of unilateral wrist pain patients was tested to assess the presence of cognitive deficits in patients that also experienced hand pain, but unrelated to CRPS. A group of shoulder pain patients was tested to assess possible effects of crossing the arms, but without moving along the painful body-part. Using a temporal order judgment task of vibrotactile pairs of stimuli on the hands, similar to that in Moseley et al. (2009), we measured the prioritization of stimuli on the painful versus the non-painful limb in each of the three patient groups. In addition, we investigated if such a perceptual bias is reversed when the arms are crossed over the body midline to assess whether any observed perceptual deficits are dependent on a somatotopic frame of reference (i.e. arm-based) or rather on a spatiotopic frame of reference that takes into account the position of the limbs (i.e. space-based). In CRPS patients, we expected a prioritization of stimuli on the non-painful hand that is reversed when arms are crossed. In wrist and shoulder pain patients, we expected the opposite: a prioritization of stimuli on the painful hand.

METHODS

PARTICIPANTS

Three patient groups were recruited from two hospitals: (1) patients with Complex Regional Pain Syndrome (CRPS) of the upper limbs, (2) patients with unilateral wrist pain and (3) pain patients with unilateral shoulder pain. In each of the three groups, patients were included when they were aged between 18 and 70 years, Dutch-speaking and had experienced unilateral upper limb pain for longer than 3 months. Patients were excluded in the presence of contralateral upper body pain, insufficiently corrected visual impairments, nerve injury, or recent (< 3 weeks) surgery of the painful limb. There were also additional criteria that were specific for each group (see 2.1.1.-2.1.3.). The study was approved by the Ethics Committee of University Hospital Ghent. All participants gave their written informed consent and received a compensation. Recruitment continued from January 2014 until May 2015.

COMPLEX REGIONAL PAIN SYNDROME

CRPS type 1 patients were clinically diagnosed by their doctor. They were also tested during the study in order to *a)* confirm the *research* diagnosis of CRPS type 1; *b)* account for differences in diagnostic criteria employed by doctors from both hospitals. Patients not meeting the criteria for the diagnosis of CRPS type 1 or reporting contralateral upper body pain at the time of the experiment were also excluded from further analysis. Sixteen CRPS-I patients (age: *M* = 51.31, SD = 11.72, range = 23-68 years; 3 men, 2 ambidextrous) took part in this study. The experiment was discontinued for one participant who was unable to perform the task adequately, and another had to be excluded due to contralateral upper limb pain at the time of the experiment. Three more participants did not meet the research criteria for the diagnosis of CRPS-I at the time of the experiment and had to be excluded as well. As a result, 11 participants were included for further analysis (age: *M* = 48.27, SD = 11.99, range = 23-66 years; 1 man; 2 ambidextrous; 3 left side painful; see http://hdl.handle.net/1854/LU-7179946 or the Appendix for a more detailed overview of recruitment and inclusion.

UNILATERAL WRIST PAIN

Patients with unilateral ulnar wrist pain (Nakamura, 2001; Shin, Deitch, Sachar, & Boyer, 2005) were invited to take part in this study. Sixteen unilateral wrist pain patients (age: *M* = 39.69, SD = 12.38, range = 24-59 years; 4 men; 5 left handed, 2 ambidextrous; 9 left side painful) participated and were screened to rule out the diagnosis of CRPS. Participants could still be excluded after the study when they reported contralateral upper body pain at the time of the experiment or when the diagnostic screening resulted in a diagnosis of CRPS. However, none of the participants had to be excluded (see http://hdl.handle.net/1854/LU-7179946 or the Appendix).

UNILATERAL SHOULDER PAIN

Patients with unilateral shoulder pain, due to frozen shoulder syndrome (J. Lewis, 2015; Robinson et al., 2012) or rotator cuff syndrome (Beaudreuil et al., 2009; Hughes, Taylor, & Green, 2008; Longo, Berton, Ahrens, Maffulli, & Denaro, 2011), were invited to participate in this study. Twenty unilateral shoulder pain patients (age: M = 52.15, SD = 7.58, range = 40-64 years; 9 men, 1 left handed, 5 ambidextrous) took part and were screened to rule of the diagnosis of CRPS. Participants could still be excluded after the study when they reported contralateral upper body pain at the time of the experiment or when they received the diagnosis of CRPS after the screening procedure. The experiment was discontinued for two participants who were unable to perform the task adequately and three more were excluded due to contralateral upper body pain at the time of the experiment. As a result, 15 participants (age: M = 51.00, SD = 8.94, range = 35-64 years; 7 men; 1 left handed, 5 ambidextrous; 6 left side painful) were included for further analysis (see http://hdl.handle.net/1854/LU-7179946 or the Appendix).

SELF-REPORT MEASURES

Participants completed an ad hoc questionnaire assessing socio-demographic characteristics, the Pain Grading Scale (PGS; Von Korff, Ormel, Keefe, & Dworkin, 1992), and a Hand Dominance Questionnaire (Van Strien, 1992). The PGS was used to assess the severity of pain complaints and pain-related disability in the patient samples, according to five grades: Grade 0 = *pain free*; Grade I = *low disability-low intensity*; Grade II = *low disability-high intensity*; Grade III = *high disability-moderately limiting*; and Grade IV = *high disability-severely limiting*. Also, after each experimental block, a series of self-report items assessed *i)* the perceived intensity of the vibrotactile stimuli on each hand (Likert scale from 0 “not intense at all” to 10 “very intense”); *ii)* to what extent they were able to concentrate during the task (Likert scale from 0 “not at all” to 10 “very well”); *iii)* to what extent they experienced the task as fatiguing (Likert scale from 0 “not at all” to 10 “very much”). At the end of the experiment, additional items assessed to what extent participants *iv)* directed their attention to the vibrotactile stimuli; *v)* made an effort to complete the task; *vi)* experienced fear/tension during the task and *vii)* found the task meaningful (all measured on a Likert scale from 0 “not at all” to 10 “very much”). Additional questionnaires that are described in the Study Protocol in the Appendix were not used for the purpose of this study and are therefore not further discussed.

DIAGNOSTIC SCREENING

In order to confirm the diagnosis of CRPS type 1 in the CRPS sample and to exclude CRPS in the wrist and shoulder pain groups, a diagnostic screening procedure was performed on all participants (see Table 2). The procedure was based on the Budapest criteria for the research diagnosis of CRPS type 1 (Harden et al., 2010). Participants received the research diagnosis of CRPS type 1 when *i)* they experienced continuing pain, which was disproportionate to any inciting event; *ii)* they *reported* at least 1 symptom in each of four symptom categories (sensory, vasomotor, sudomotor/edema, motor/trophic); *iii)* they *displayed* minimum 1 symptom in at least two of four sign categories (sensory, vasomotor, sudomotor/edema, motor/trophic); and *iv)* there was no other diagnosis that better explained the signs and symptoms. The first and last criterion were evaluated by the responsible doctor, the second and third were assessed by the experimenter by, respectively, interviewing and testing the participants.

SELF-REPORTED SYMPTOMS

Participants were asked by the experimenter which of the following symptoms they experienced from the four symptom categories: hyperesthesia and/or allodynia (sensory category), temperature asymmetry and/or skin color changes and/or skin color asymmetry (vasomotor category), edema and/or sweating changes and/or sweating asymmetry (sudomotor/edema category), and decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin) (motor/trophic category).

DISPLAYED SIGNS

The experimenter assessed which of the following symptoms from the four sign categories were present at the time of the experiment: hyperalgesia (to pinprick) and/or allodynia (to heat/cold and to brush stroking) (sensory category), temperature asymmetry and/or skin color changes and/or skin color asymmetry (vasomotor category), edema and/or sweating changes and/or sweating asymmetry (sudomotor/edema category), and decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin) (motor/trophic category).

SENSORY SYMPTOMS

Hyperalgesia was assessed by subsequently pricking the non-painful and the painful limb twice with a Semmes-Weinstein monofilament no. 19 (SENSELab Aesthesiometer, Hörby, Sweden). Participants reported pain intensity both times on a Likert scale ranging from 0 ("no pain") to 10 ("worst imaginable pain"). The symptom was evaluated as positive when the maximal pain rating of the painful limb minus the maximal pain rating of the non-painful limb ≥ 3. Thermal allodynia was measured by subsequently rolling a cold (25°C) and a warm (40°C) metal roller (SENSELab™, Rolltemp, Hörby, Sweden) twice over the non-painful and the painful limb (SenseLab, n.d.-a). The experimenter also stroked (~2s, ~5cm distance) these locations twice with a small brush (~22mm wide) to measure brush allodynia (SenseLab, n.d.-b). Pain intensity was reported twice for each hand on a Likert scale ranging from 0 ("no pain") to 10 ("worst imaginable pain"). Thermal and brush allodynia were considered present when the maximal pain rating of the painful limb minus the maximal pain rating of the non-painful limb ≥ 3.

VASOMOTOR SYMPTOMS

An infrared thermometer (Hartmann, Thermoval® duo scan, Heidenheim, Germany) was used to measure the temperature of the painful and the non-painful limb. Based on Perez (Perez, Keijzer, Bezemer, Zuurmond, & de Lange, 2005), temperature asymmetry was defined as a difference of 0.4°C or more between both limbs (in either direction). Changes and/or asymmetry in skin color were assessed by observing the painful and non-painful limb.

SUDOMOTOR SYMPTOMS/EDEMA

The circumference of both hands and wrists was measured with a flexible measuring tape (SECA). Edema was defined as a minimal difference in circumference of 6.5% between the painful and the non-painful limb (Perez et al., 2005). Sweating changes and/or asymmetry were assessed by observing and touching the skin of the painful and non-painful limb.

MOTOR/TROPHIC SYMPTOMS

Dorsal and palmar flexion (degrees in °) of the wrist was measured with an inclinometer (BASELINE®) and added up to calculate the active range of motion (AROM). A decreased AROM was present when the AROM of the painful limb was more than 15% smaller than the AROM of the non-painful limb (Perez et al., 2005). Motor dysfunctions (tremor, weakness and dystonia) and trophic changes of the nails, hair and skin were assessed through observation.

STIMULI AND APPARATUS

Participants were seated in a dimly lit room with their hands, palms down, resting on a table (see Figure 1). The distance between the edge of the table, near the trunk, and the index fingers was 35cm and the distance between both index fingers was 40 cm. At a distance of 35 cm in front of the index fingers, a red fixation LED prevented participants from shifting their gaze during the task. The participant's head was also fixated using a chin wrest. To protect them from any auditory distraction, all participants wore headphones through which continuous white noise (46dB) resounded. The experimenter was sitting opposite to and facing the participant.

VIBROTACTILE STIMULI

On the sensory territory of the superficial radial nerve of each hand, two magnet linear actuators (C-2 TACTOR, Engineering Acoustics, Inc., Florida) were attached that released vibrotactile stimuli (10ms duration, 200Hz). The actuators were driven by self-developed software and a controlling device that converted electrical signals (Watt) into oscillating movements of the actuators against the skin. The

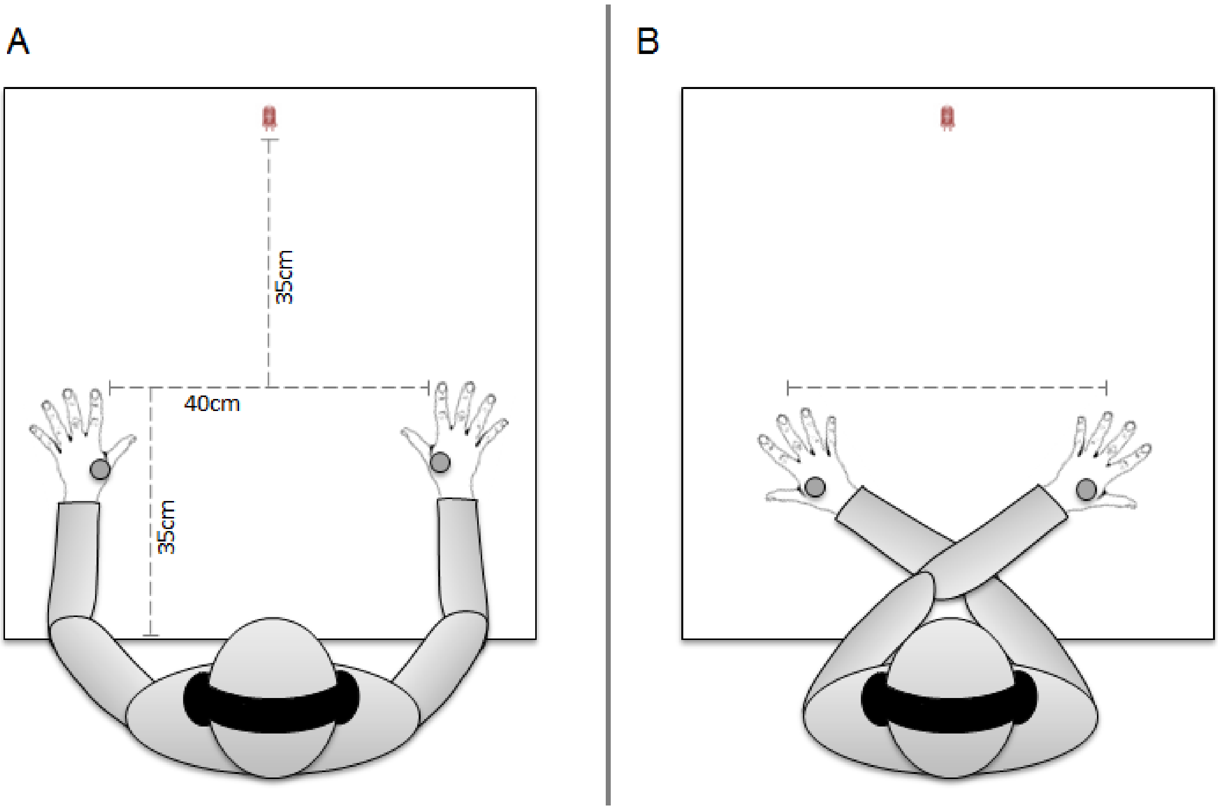

FIGURE 1. Experimental set-up of the TOJ task. Panel A: uncrossed arms condition. Panel B: crossed arms condition.

intensity of the vibrotactile stimuli were determined individually and matched between both hands by means of a double random staircase procedure, based on the ‘simple up-down method’ of Levitt (Levitt, 1971). In the first part of the staircase procedure, 16 stimuli presented on the left hand were judged relative to a reference stimulus with maximum intensity (power = 0.21Watt) on a 5-point Likert scale ranging from 1 (“almost no sensation”) to 5 (“maximum intensity”). The intensity that corresponded to an average rating of 3 was selected as the stimulus intensity for the left hand and served as the reference stimulus for the second part of the staircase procedure. In the second part, another 16 stimuli were presented, now to the right hand, and were compared to the selected 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 resulted in an averaged rating of 3 was selected as the intensity for stimuli on the right hand.

PROCEDURE

In the first phase of the study, participants completed the socio-demographic questionnaire, the Pain Grading Scale and the Hand Dominance Questionnaire. In the second phase, participants were seated and underwent the diagnostic screening procedure (interview + testing) to assess the diagnosis of CRPS. In the third phase of the study, the experimenter attached the actuators to the hands and gave the participants instructions about the staircase procedure. Following this, the headphones were turned on and the staircase procedure initiated. First, participants were asked to judge the intensity of a series of vibrotactile stimuli on their left hand to a reference stimulus of maximal intensity on the left hand, on a 5-point Likert scale from 1 (“almost no sensation”) to 5 (“maximal sensation”). Second, participants had to compare the intensity of a series of vibrotactile stimuli on their right hand to a reference stimulus of moderate intensity 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”). Responses were inserted manually on a keyboard by the experimenter. As soon as the staircase procedure was finished, headphones were temporarily removed.

In the temporal order judgment (TOJ) task, participants were required to judge the temporal order of two stimuli, one presented to either hand. First, they were instructed to fixate on the red fixation LED in front of them, to place their chin in the chin wrest and to keep their hands still on the table throughout the task. After receiving these instructions, headphones were turned back on. The TOJ task started with three practice blocks of increasing difficulty. In the first practice block (8 trials), participants were administered only one tactile stimulus in each trial (4 left and 4 right, divided randomly) and were asked to locate it (“left” versus “right”) in order to practice response mapping. In the second practice block (12 trials), participants had to judge the temporal order (“left first” versus “right first”) of two tactile stimuli, administered to either hand and separated by 3 different stimulus onset asynchronies (SOA’s) of ±200, ±90 or ±55ms (negative values indicating that the left hand was stimulated first) (Gallace & Spence, 2005). In the third practice block (18 trials), participants did the same as in practice block 2 but with their arms crossed (which arm was on top was counterbalanced). When deemed necessary by the experimenter, practice blocks were repeated until performance was satisfactory. In addition, participants could only proceed from the third practice block to the first experimental block when a minimal performance of 75% was achieved on trials with the highest SOA (±200ms).

The experimental design of the TOJ study is illustrated in Figure 2. In four experimental blocks (each 60 trials), participants judged the temporal order of two tactile stimuli, one administered to the left hand, one on the right. The position of the arms was either uncrossed or crossed in the first block (counterbalanced) and alternated between blocks. SOA's differed between ±200, ±90, ±55, ±30 and ±10ms and were divided randomly and equiprobably within blocks (Gallace & Spence, 2005). Each trial started with the illumination of the red fixation LED, followed by the tactile stimuli on the hands. Participants reported verbally on which hand they perceived the first stimulus ("left hand" versus "right hand"), regardless of arm position. The experimenter inserted these responses manually on a keyboard (a = "left side first", p = "right side first"). Accuracy was emphasized over speed, although participants were advised to try maintaining a steady pace in responding. After each experimental block, participants filled in the post-block items and temperature was reassessed on the back of both hands.

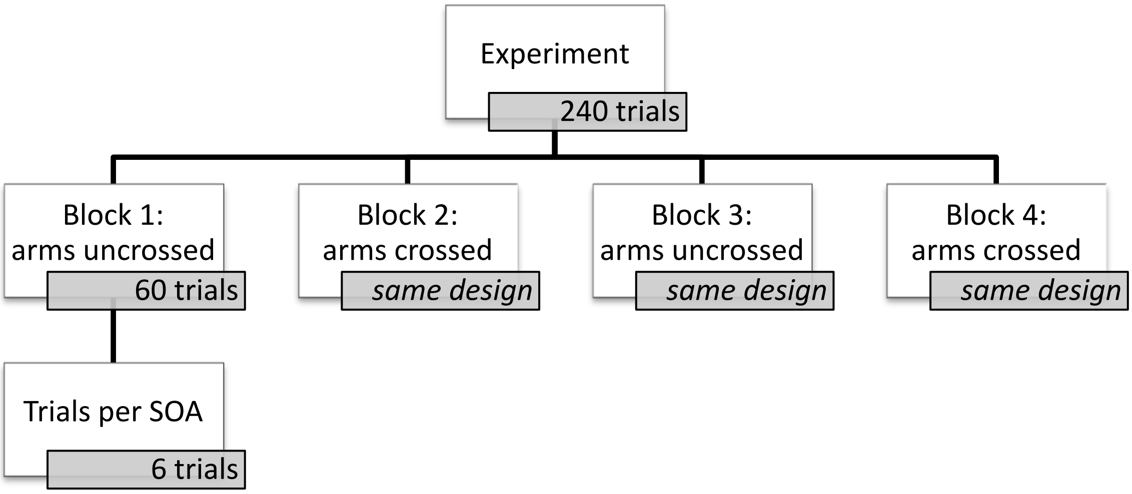

FIGURE 2. Experimental design of TOJ study. All patient groups performed the same TOJ experiment. Arm position was either crossed or uncrossed during the first block and alternated between blocks.

TOJ MEASURES

Based on the procedure of Spence, Shore and Klein (2001), the proportion of trials on which participants perceived the tactile stimulus on their painful limb first was calculated for each participant, for each SOA and for each condition (crossed vs. uncrossed arm position). A sigmoid function was then fitted to these proportions and a standardized cumulative normal distribution (probits) was used to convert the proportion of left hand/right hand first responses (left hand first when the left hand/wrist/shoulder was painful, right hand first when the right hand/wrist/shoulder was painful) into a z-score. The best-fitting straight line was computed for each participant and for both conditions (crossed vs. uncrossed arm position) and the derived slope and intercept were used to calculate 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 tactile stimuli (on the left and right hand) as occurring first equally often. This point can be interpreted as the SOA value that corresponds to a 0.5 proportion of left hand/right hand first responses (Spence et al., 2001). The PSS is calculated by taking the opposite of the intercept and dividing this by the slope, both derived from the best-fitting straight line. To simplify the interpretation, the sign of the PSS was inversed for participants with pain on the right hand/wrist/shoulder. As such, the PSS indicates how much time the stimulus on the non-painful limb had to presented before/after the stimulus on the painful limb, in order to be perceived as simultaneous. A positive PSS thus reflects the prioritization of stimuli on the painful limb, regardless of arm position (crossed vs. uncrossed).

The JND indicates the interval between both tactile stimuli (on the left and right hand) needed to achieve a 75% correct performance and, as such, provides a standardized measure of the sensitivity of participants' temporal perception. It is calculated by dividing 0.675 by the slope of the best-fitting straight line (Spence et al., 2001) and corresponds to the value obtained by subtracting the SOA at which the best fitting straight line crosses the 0.75 point from the SOA at which the same line crosses the 0.25 point, and dividing it by 2.

ANALYSES

Participants were excluded from the analyses if one of their PSS values was greater/smaller than twice the largest SOA (i.e. ±400ms), or if their performance (% correct answers) for the largest SOA (i.e. ±200ms) in one of the conditions was below 75%. In total, 8 participants did not meet these criteria, but only in the crossed condition, as the task was considerably more difficult with crossed arms than in a normal, uncrossed position. Therefore, PSS and JND data from these 8 participants were only excluded for the analysis of the crossed condition. It concerns two CRPS patients who had a PSS greater than 400, three wrist pain patients who performed below 75% and three shoulder pain patients, two who had a PSS value over 400 and one who had both a performance below 75% and a PSS over 400. As such, only a smaller sample of 9 CRPS patients, 13 wrist pain patients and 12 shoulder pain patients (crossed data sample, n = 34) was included for the analysis of the crossed condition, whereas a larger sample of 11 CRPS patients, 16 wrist pain patients and 15 shoulder pain patients (uncrossed data sample, n = 42) was included for all other analyses.

To investigate whether there was a prioritization of stimuli on the painful limb – or rather the non-painful limb, one-sample *t*-tests were performed to test if the PSS values in the crossed and uncrossed condition differed significantly from 0ms. In addition, a One-way Analysis of Variance (ANOVA) with *Group* (CRPS vs. wrist pain vs. shoulder pain) as between-subject factor was performed to compare the PSS values in the uncrossed condition between patient groups. Finally, a Repeated Measures Analysis of Variance (RM ANOVA) with *Condition* (crossed vs. uncrossed) as within-subject factor and *Group* (CRPS vs. wrist pain vs. shoulder pain) as between-subject factor compared the PSS and JND values between both conditions and between patient groups. Linear Regression Analysis was used to test whether the PSS in both conditions could be predicted by pain intensity and duration, and by temperature differences between the painful and non-painful limb measured immediately after each block. The significance level was set at $p < 0.05$.

RESULTS

PARTICIPANTS

An overview of patient characteristics is presented in table 1 and results from the diagnostic screening can be found in table 2. Although screening results were missing for 4 shoulder pain patients, it is very unlikely that these participants would have met the criteria for the diagnosis of CRPS as they never received the diagnosis of CRPS and also did not report pain on the upper extremities.

Patient characteristics	CRPS (n=11)		Wrist pain (n=16)		Shoulder pain (n=15)	
Gender	N	%	N	%	N	%
Male	1	9.09	4	25.00	7	46.67
Female	10	90.91	12	75.00	8	53.33
Hand dominance						
Left	0	0.00	5	31.25	1	6.67
Right	9	81.82	9	56.25	9	60.00
Both	2	18.18	2	12.50	5	33.33
Pain Laterality						
Left	3	27.27	9	56.25	6	40.00
Right	8	72.73	7	43.75	9	60.00
PGS						
0	0	0.00	0	0.00	0	0.00
I	1	9.09	4	25.00	0	0.00
II	0	0.00	2	12.50	7	46.67
III	5	45.45	2	12.50	1	6.67
IV	5	45.45	7	43.75	7	46.67
	Mean	SD	Mean	SD	Mean	SD
Age (years)	48.27	11.99	39.69	12.38	51.00	8.94
Pain intensity (0-10)	5.27	2.53	3.93	2.66	4.53	2.61
Pain duration (months)	7.65	7.28	24.33	28.18	23.80	17.02
Temperature diff. (°C)	-0.10	0.40	-0.03	0.22	-0.05	0.16

TABLE 1. Overview of patient characteristics for each patient group. ‘Hand dominance’ based on Hand Dominance Questionnaire. ‘PGS’, Pain Grading Scale. PGS missing for 1 wrist pain patient. ‘Pain intensity’ measured at the beginning of the experimental session. ‘Temperature difference’ between painful and non-painful hand, based on diagnostic screening (missing for 1 wrist pain and 4 shoulder pain patients).

Budapest research criteria for CRPS-I	CRPS	Wrist pain	Shoulder pain
1. Continuing pain, disproportionate to any inciting event	**11/11**	**15/16**	**7/11**
2. Reporting at least one symptom in all categories	**11/11**	**12/16**	**1/11**
Sensory:			
Allodynia	10/11	11/16	1/11
Hyperesthesia	8/11	11/16	5/11
Vasomotor:			
Temperature asymmetry	9/11	12/16	3/11
Skin color changes/asymmetry	10/11	11/16	1/11
Sudomotor/edema:			
Edema	10/11	13/16	2/11
Sweating changes/asymmetry	3/11	2/16	0/11
Motor/trophic:			
Decreased range of motion	11/11	15/16	10/11
Motor dysfunction	11/11	16/16	9/11
Trophic changes	7/11	7/16	0/11
3. Displaying at least one sign at time of evaluation in two or more categories	**11/11**	**4/16**	**0/11**
Sensory:			
Hyperalgesia	9/11	3/16	0/11
Thermal allodynia	7/11	3/16	0/11
Brush allodynia	4/11	2/16	0/11
Vasomotor:			
Temperature asymmetry	3/11	2/15[a]	0/11
Skin color changes/asymmetry	6/11	0/16	0/11
Sudomotor/edema:			
Edema	1/11	0/16	0/11
Sweating changes/asymmetry	1/11	0/16	0/11
Motor/trophic:			
Decreased range of motion	10/11	10/16	2/11
Motor dysfunction			
Tremor	1/11	0/16	0/11
Weakness	10/11	4/16	3/11
Dystonia	2/11	0/16	0/11
Trophic changes			
Hair	2/11	3/16	0/11
Nails	2/11	3/16	0/11
Skin	6/11	2/16	0/11
4. No other diagnosis that better explains the signs and symptoms	**11/11**	**3/16**	**0/11**
DIAGNOSIS CRPS	**11/11**	**0/16**	**0/11**

TABLE 2. Results from diagnostic screening in each patient group. [a] missing value for one participant.

SELF-REPORT MEASURES

The results of the PGS are illustrated in Table 1. The mean perceived intensity of the vibrotactile stimuli was low and did not differ between the left and the right hand (left hand: M = 2.66, SD = 2.68; right hand: M = 3.04, SD = 2.48; F(1,41) = 2.46, p = 0.125). Participants reported directing their attention to a large extent to the vibrotactile stimuli (M = 7.83, SD = 2.30). They reported that they were able to concentrate well during the task (M = 7.22, SD = 1.77) and that they found the task only mildly fatiguing (M = 2.73, SD = 2.38). Participants made a large effort to complete the task (M = 8.02, SD = 1.82), reported finding the task very meaningful (i.e. not having to guess; M = 8.00, SD = 1.47) and reported little fear/tension during the task (M = 1.93, SD = 2.16). There were no significant differences between the three patient groups.

TACTILE INTENSITIES

The mean intensity (Watt) of the tactile stimuli, derived from the staircase procedure, was not significantly different between the left and the right hand (left: M = 0.094, SD = 0.023; right: M = 0.093, SD = 0.045; F(1,39) = 0.02, p = 0.905) in neither of the groups (F(2,39) = 1.51, p = 0.233). There were also no differences in intensity of the tactile stimuli between the painful and the non-painful hand (painful: M = 0.096, SD = 0.043; non-painful: M = 0.091, SD = 0.027; F(1,39) = 0.62, p = 0.435) in either of the groups (F(2,39) = 0.37, p = 0.691).

PSS AND JND VALUES: ARMS UNCROSSED

PSS and JND values of the uncrossed condition are displayed in Table 3. One-sample t-tests revealed that in neither patient group, PSS values significantly differed from zero (CRPS: M = -2.38, SD = 58.85, t(10) = -0.13, p = 0.896; wrist pain: M = -1.46, SD = 36.78, t(15) = -0.16, p = 0.876; shoulder pain: M = -10.33, SD = 38.08, t(14) = -1.05, p = 0.311). Also, The One-way ANOVA indicated that PSS values in the uncrossed condition did not differ between *Groups* (F(2,39) = 0.18, p = 0.834) (see Figure 3).

Group	PSS - uncrossed	PSS - crossed	JND - uncrossed	JND - crossed
CRPS				
2	114,39	[b]	-98,92	[b]
3	46,24	-117,88	-49,97	-142,93
4	-21,31	-2,51	-99,79	-170,71
6	-4,43	46,80	-54,76	-99,40
7	74,73	-50,62	-65,45	-124,37
8	-1,43	-96,47	-54,64	-933,01
11	-15,77	32,24	-76,22	-184,05
12	-74,64	-117,21	-69,14	-124,88
13	-37,88	[b]	-52,32	[b]
15	-69,37	5,39	-62,99	-165,12
16	-36,72	18,37	-63,63	-72,93
Mean	*-2.38*	*-31.32*	*-67.98*	*-224.16*
SD	*58.85*	*65.46*	*17.35*	*268.16*
Wrist pain				
1	-32,57	-100,40	-50,15	-198,07
2	-6,95	18,38	-49,73	-68,73
3	45,80	-149,68	-96,97	-148,48
4	-50,71	[a]	-61,87	[a]
5	82,09	68,69	-56,77	-162,51
6	27,21	[a]	-63,60	[a]
7	-24,76	-92,10	-72,90	-164,16
8	2,49	-52,36	-57,47	-190,26
9	-19,33	-15,55	-43,48	-51,24
10	-12,95	51,62	-55,37	-116,11
11	21,34	219,82	-56,36	-1813,33
12	-30,16	-15,50	-74,10	-81,78
13	18,39	[a]	-44,65	[a]
14	-61,89	-71,37	-65,19	-119,93
15	-0,69	11,35	-43,59	-56,80
16	19,41	-51,79	-65,84	-380,71
Mean	*-1.46*	*-13.76*	*-59.88*	*-273.24*
SD	*36.78*	*93.84*	*13.76*	*470.68*
Shoulder pain				
1	17.41	47.88	-50.62	-202.15
2	27.36	[a,b]	-58.68	[a,b]
3	10.35	-97.21	-50.66	-293.72
4	2.30	51.43	-59.87	-118.32
7	-13.46	-32.08	-51.07	-105.97
8	-16.58	113.06	-52.75	-194.43
9	11.64	-51.93	-76.68	-118.72
10	-6.20	26.61	-63.34	-92.22
11	-85.19	[b]	-68.26	[b]
12	11.75	29.47	-70.81	-233.56
13	10.50	-67.12	-56.25	-139.61
14	-98.18	[b]	-93.57	[b]
16	-11.94	19.42	-48.80	-60.90
19	-44.23	-113.57	-56.55	-182.77
20	29.46	-10.56	-66.81	-186.86
Mean	*-10.33*	*-7.05*	*-61.65*	*-160.77*
SD	*38.08*	*67.26*	*12.15*	*66.52*

TABLE 3. Individual PSS and JND values for each condition. PSS = point of subjective simultaneity. JND = just noticeable difference. A positive PSS reflects attentional prioritization of stimuli on the painful limb, irrespective of hand position. Participants who were excluded from the analysis of the crossed condition are marked with [a] when performance on crossed trials with the highest SOA (±200ms) was < 75% and/or with [b] when |PSS crossed condition| > 400

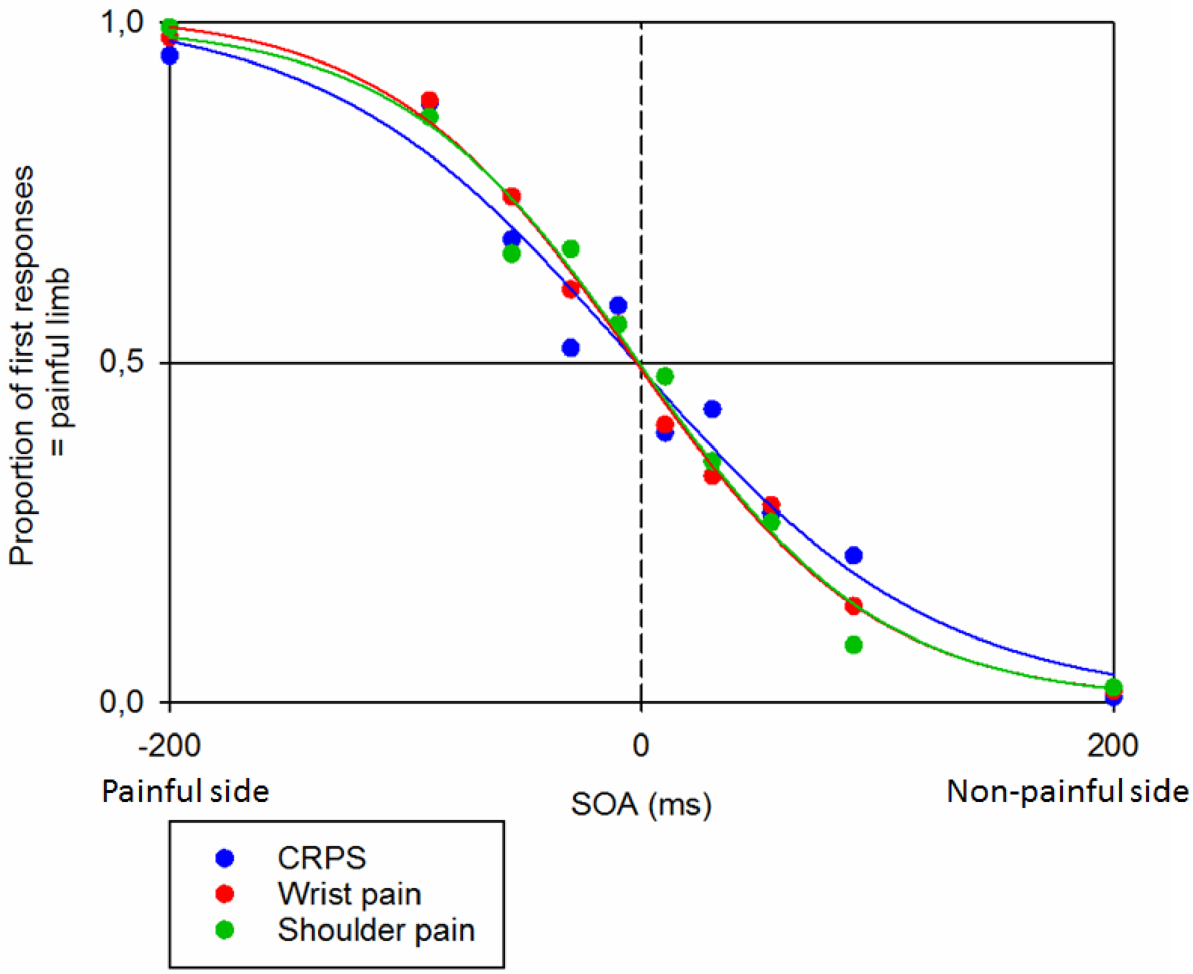

FIGURE 3. Sigmoid plot, illustrating PSS shifts towards the painful or non-painful side in the uncrossed condition. The figure illustrates the fitted curves from the cumulative data of 11 CRPS, 16 wrist pain and 15 shoulder pain patients included in this study (uncrossed data sample). The *x*-axis represents the SOAs between each pair of tactile stimuli presented to the hands. As the aim of the study was to evaluate the effect of unilateral pain (left or right) on the TOJ for tactile stimuli, the responses were re-coded in a way that negative values on the left side of the *x*-axis indicate that the painful hand was stimulated first, whereas positive values indicate that the non-painful hand was stimulated first. The *y*-axis shows the mean proportion of responses indicating that the painful hand was perceived as having been stimulated first. In each of the groups, the PSS is close to zero, reflecting the absence of perceptual biases towards or away from the painful hand.

PSS AND JND VALUES: ARMS CROSSED

PSS and JND values of the crossed condition are displayed in Table 3. As discussed earlier, only a smaller sample (n = 34) of participants was used to perform the following analyses of the crossed condition. One-sample t-tests showed that in none of the groups, PSS values differed from zero (CRPS: M = -31.32, SD = 65.46, $t(8) = -1.44$, $p = 0.189$; wrist pain: M = -13.76, SD = 93.84, $t(12) = -0.53$, p = 0.607; shoulder pain: M = -7.05, SD = 67.26, $t(11) = -0.36$, $p = 0.723$). There were also no differences in PSS values between *Groups* ($F(1,2) = 0.44$, $p = 0.649$). The difference between the crossed and the uncrossed *Condition* was not significant ($F(1,31) = 0.84$, $p = 0.368$). The RM ANOVA indicated that the interaction effect between *Condition* and *Group* was not significant ($F(2,31) = 0.06$, $p = 0.941$).

Analyses of the JND values only revealed a main effect of *Condition* on the JND ($F(1,31) = 7.71$, $p < 0.01$), suggesting that the task was more difficult when the arms were crossed (M = -220.55, SD = 319.16) than when they were uncrossed (M = -61.43, SD = 12.99).

PATIENT CHARACTERISTICS AND CLINICAL ASSESSMENT

Based on similar studies, additional analyses were done to explore the relation between the PSS and demographic/clinical variables, such as pain duration, pain laterality, pain intensity during the experiment, hand dominance and temperature differences between the painful and non-painful limb. Correlations are reported in Table 4.

	CRPS		Wrist pain		Shoulder pain	
Variables	PSS C	PSS UC	PSS C	PSS UC	PSS C	PSS UC
Pain intensity during experiment (0-10)	.15	.25	.21	.53*	.32	.13
Pain duration (months)	.73*	.13	.26	.47	.21	.08
Skin temperature difference UC (°C)	-	.12	-	.14	-	.08
Skin temperature difference C (°C)	.48	-	.58	-	.36	-

TABLE 4. Correlations between clinical assessments and PSS values in each condition (crossed vs. uncrossed). Pain intensity was averaged over each of the four experimental blocks. Skin temperature differences between the painful and the non-painful hand were measured after each crossed (C) and uncrossed (UC) block and averaged over equivalent blocks. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

In the CRPS group, PSS values in the crossed arms condition were related to the duration of pain complaints (r = 0.73, F(1,7) = 7.89, p = 0.026), that is, each additional month of pain complaints could be expected to result in a decrease of the PSS value of about 6ms (unstandardized B = -5.915, t = -2.83, p =0.026). This relation was not significant in the uncrossed condition. The PSS was not related to any of the other variables in the CRPS group.

In the wrist pain group, the duration of pain complaints was, similarly but less strong, related to the PSS in the uncrossed condition (r = 0.47, F(1,14) = 3.87, p = 0.069). For every additional month these patients experienced pain, the stimuli on the painful limb needed to be presented about 2ms ahead of the stimuli on the non-painful limb, in order to be perceived as simultaneous (unstandardized B = -0.606, t = -1.97, p = 0.069). This was not the case for the crossed condition. There was also a negative relation between mean pain intensity during the experiment and the PSS when arms were uncrossed (r = 0.53, F(1,14) = 5.41, p = 0.036), but not when they were crossed. For each increase in pain intensity, measured on a scale from 0 to 10, the stimuli on the painful limb needed to be presented about 7ms before the stimuli on the non-painful limb to be perceived as simultaneous (unstandardized B = -6.990, t = -2.33, p = 0.036). The relation between temperature differences – defined as the difference in temperature between the painful and the non-painful hand as measured after each experimental block – and the PSS was marginally significant in the crossed condition (r = 0.58, F(1,9) = 4.64, p = 0.060), but not for the uncrossed condition. For each 0.1°C the painful limb was colder than the non-painful limb, the stimuli on the painful limb needed to be presented about 23ms earlier than those on the non-painful limb to be perceived as equal. The PSS was not related to pain laterality or hand dominance (not significant). Finally, in the shoulder pain group, the PSS was unrelated to all variables.

DISCUSSION

The goal of this study was to replicate earlier findings (Moseley et al., 2009) of cognitive deficits in CRPS patients and to investigate the specificity of these deficits for CRPS, compared to other chronic pain populations. A temporal order judgment

(TOJ) task was used to compare the perceptual bias of tactile stimulation on the painful versus the non-painful limb in each condition (crossed vs. uncrossed) and in each group (CRPS vs. wrist pain vs. shoulder pain). According to the literature, we expected a bias *away* from the painful hand in CRPS patients and a bias *towards* the painful hand in the pain control groups. In addition, we expected the bias in CRPS patients to reverse when arms were crossed.

In general, the results of this study could not confirm the presence of perceptual biases in CRPS patients. The mean PSS was close to zero, reflecting the absence of a consistent perceptual bias throughout the CRPS group. A significant number of CRPS patients did seem to prioritize stimuli on the non-painful hand (negative PSS value), to the detriment of stimuli on the painful hand, but large variability was present between individuals. In the wrist pain group, no consistent evidence was found either for a perceptual bias towards or away from the painful hand (mean PSS close to zero). Again individual differences in PSS values were quite large, restraining us from drawing definite conclusions about the presence or absence of perceptual biases in this chronic pain population. In the shoulder pain group, we also expected a perceptual bias towards the painful arm. However, we could not find evidence for this hypothesis: no significant perceptual bias was found towards the hand of the painful arm. In addition, crossing the arms had little effect on the PSS values in any of the groups, except that they were somewhat larger. This might be explained by the increased difficulty of the task in the crossed position, also known as the ‘crossed hands deficit’ (Shore, Spry, & Spence, 2002), as suggested by the JND and self-reports. It is therefore not possible to conclude from these data whether perceptual biases in chronic pain populations are space-based or arm-based.

The fact that the cognitive bias was not consistent throughout the whole CRPS sample might be related to other variables, such as pain duration and pain intensity. In fact, we found that the longer patients had suffered from CRPS, the more they prioritized stimuli on the non-painful hand during the crossed condition. Importantly, this relation was not caused by increased difficulty performing the task (i.e. higher JND) at longer symptom durations. Given the rather short symptom duration of patients in our CRPS sample, compared to other studies (Frettlöh et al., 2006; Kolb et al., 2012; Moseley et al., 2009; Reid et al., 2016), stronger cognitive biases could have been expected in a more chronic CRPS group. Similar to the CRPS group, but less explicit, longer symptom duration was related to a lower PSS – i.e. prioritization of stimuli on the non-painful limb – in the wrist pain group. In addition, the PSS of wrist pain patients was related to pain intensity during the experiment, meaning that more pain during the TOJ task was reflected in a stronger prioritization of stimuli on the non-painful hand. Similar to what Moseley et al. (2009) found in CRPS patients, we detected a marginally significant relation in wrist pain patients between PSS values in the crossed condition and differences in temperature between the painful and the non-painful hand in that condition: relatively colder painful hands were related to negative PSS values. In shoulder pain patients, PSS values were not related to pain intensity and duration nor to temperature of the hands. These results at least suggest that neglect-like perceptual biases might not be specific to CRPS and could be determined by factors such as pain intensity, pain duration and temperature of the painful body-part. However, we should be careful in interpreting these findings, as they were not expected a priori, but were only obtained in a further exploration of the role of individual difference variables.

In sum, the results of this study could not support our hypotheses on the existence of perceptual biases away from the painful limb in CRPS patients and biases towards the painful limb in non-CRPS pain controls. None of the groups showed consistent biases in perception. However, variability within the groups was large, suggesting that other factors, such as pain intensity and duration of symptoms, might play a role in the development of cognitive deficits in CRPS, but possibly also in other pain populations. Additional studies are needed that take these variables into account by, for example, comparing perceptual biases in CRPS (and non-CRPS) patients in an acute versus a chronic pain state.

There were some limitations to this study. First, wrist and shoulder pain control groups were not individually matched to the CRPS group, due to difficulties in recruiting these patient groups. Performance on the TOJ task was therefore not equivalent in all groups, most likely due to age differences. Nevertheless, there were no differences between groups in measures of perceptual biases. Moreover, exclusion of participants with a performance below the criterion of 75% prevented the absence of individual matching from confounding the results. Second, JND values were very high in all three groups, especially in the crossed condition. The fact that the JND of some patients was larger than the highest SOA (200ms) indicates that participants did not succeed in performing the TOJ task, as it means that an interval longer than the largest actual interval (SOA) was needed to detect the order of the tactile stimuli. Literature does not yet provide guidelines for excluding participants with high JND values. For future studies, participants with JND values higher than the largest SOA could be excluded from the analyses. Third, due to the small sample sizes, the power was rather low to tests the significance of the PSS values and the relation between PSS values and patient characteristics/clinical assessments. Although the sample size was very similar to that in Moseley et al. (2009), future studies should include larger samples or adopt single-case research paradigms to account for individual differences. Fourth, only one single task, the TOJ task, was used in this study to investigate neglect-like symptoms in CRPS. However, conflicting findings on cognitive deficits in CRPS still need to be resolved, possibly by incorporating multiple tests for neurocognitive dysfunctions (e.g. line bisection and body recognition tasks) (Förderreuther et al., 2004; Kolb et al., 2012).

Reid et al. (2016) reported a series of studies using multiple measurements and attempted to reconcile conflicting results on neglect-like symptoms in CRPS. They made suggestions that could explain typical CRPS features such as distorted representations of healthy and affected limbs (Di Pietro et al., 2013) and impaired tactile acuity on the painful hand (Catley, O'Connell, Berryman, Ayhan, & Moseley, 2014). They explained visuospatial biases *towards* the affected limb in line bisection tasks and processing biases *away* from the affected limb of body-relevant stimuli (e.g. tactile stimuli) by underlining the protective function of pain. They argue that pain urges us to protect the body by visually scanning the environment and by restricting movements, translating into *i)* enhanced visuospatial representations of the space in which pain is situated and *ii)* and immobilization (spontaneous or applied) and compensatory use of the healthy limb (Catley et al., 2014) found in CRPS. Studies such as these are certainly a step forward for better understanding cognitive deficits in CRPS patients but still need validation from replication studies.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest related to the present study.

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APPENDIX:

CRPS STUDY PROTOCOL

1. Goal

The goal of this study was to investigate processes of spatial attention in patients with complex regional pain syndrome (CRPS). Recently, neglect-like symptoms were found in CRPS patients, similar to those found in post-stroke brain-damaged patients (Moseley, Gallace, & Spence, 2009). Interestingly, this tendency to neglect tactile stimulation on the affected arm reversed when participants were asked to cross their arms. This pointed to a deficit in spatial attention processing, anchored to the region of space where the affected hand normally resides. In other words, it seems that the deficit was based on a spatiotopic frame of reference, rather than a somatotopic frame of reference. However, findings on this topic are scarce and inconsistent. This study aims to replicate the study of Moseley, Gallace and Spence (2009) and compare the group of CRPS patients to a group of unilateral wrist pain patients and a group of unilateral shoulder pain patients.

2. Recruitment of patients with Complex Regional Pain Syndrome

Recruitment procedure:

Patients with complex regional pain syndrome (CRPS) were recruited by Prof. Hollevoet of the Orthopedics Department of the University Hospital Ghent and by dr. Jacobs of the Department of Rehabilitation of Maria Middelares Hospital (AZMMSJ) in Ghent. The doctor addressed supposedly eligible patients during consultation about the study and asked these patients permission to have the experimenter call them. The experimenter called interested patients to give more information about the study and were invited to the hospital to participate in the study.

Inclusion criteria:

- Age 18-70yrs
- Dutch-speaking
- CRPS, type I (duration > 3 months; situated on the hand/arm)

Exclusion criteria:

- Contralateral upper body pain complaints
- Presence of nerve injury (e.g. CRPS, type II)
- Recent surgery (< 3 weeks) at painful hand
- Insufficiently corrected visual impairments

Post-experimental exclusion criteria for analysis:

- Contralateral upper body pain complaints at time of experiment
- Absence of research diagnosis of CRPS at time of experiment, based on diagnostic screening

Additional post-experimental exclusion criteria for analysis

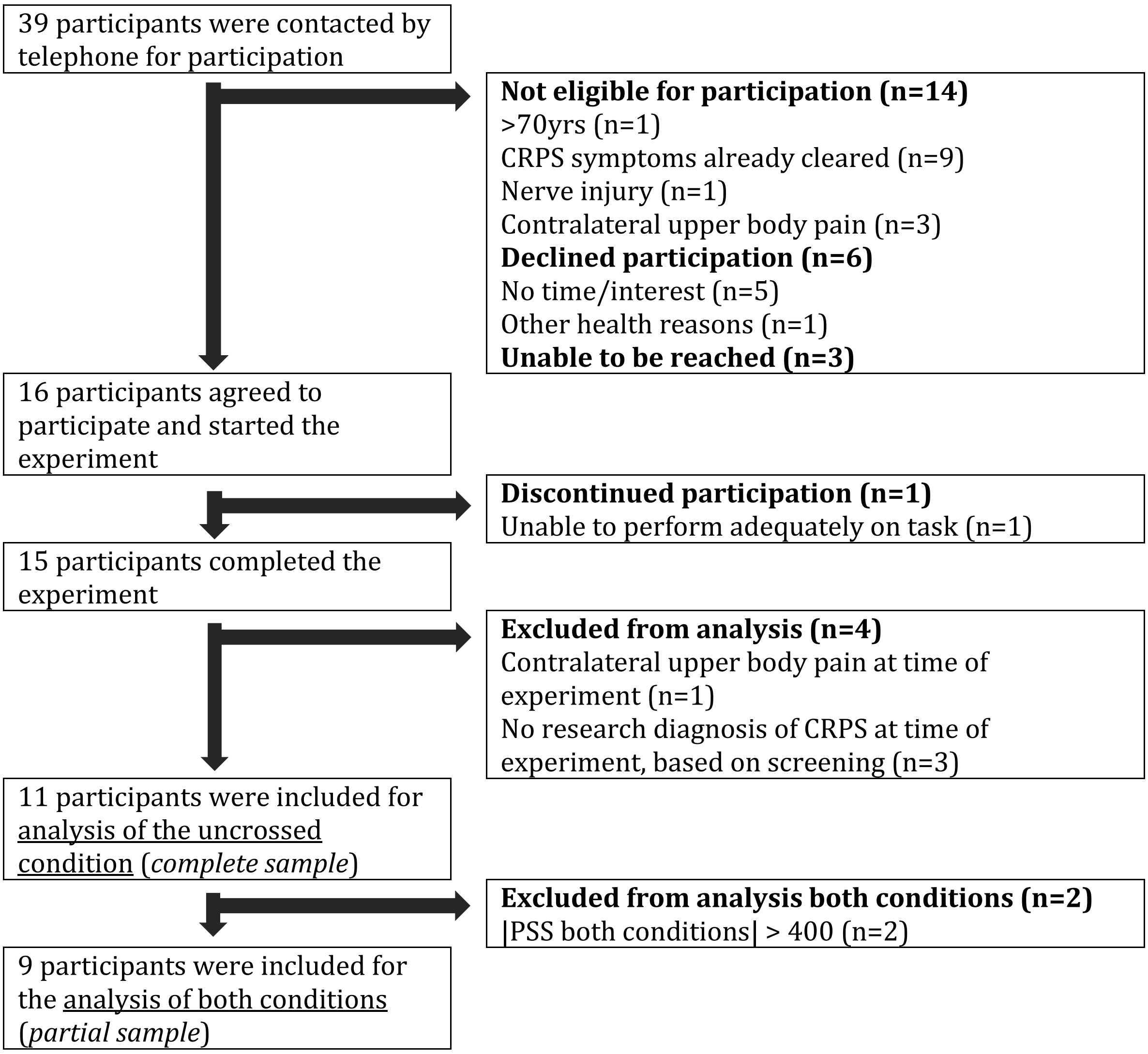
- |PSS| uncrossed condition > 400 only
- Performance on trials with highest SOA (200/-200ms) in uncrossed condition < 75%

analysis uncrossed condition (complete sample)

- |PSS| both conditions > 400
- Performance on trials with highest SOA
- (200/-200ms) in both conditions < 75%

analysis both conditions (partial sample)

Flow-chart recruitment/inclusion CRPS patients:



39 participants were contacted by telephone for participation

Not eligible for participation (n=14)
>70yrs (n=1)
CRPS symptoms already cleared (n=9)
Nerve injury (n=1)
Contralateral upper body pain (n=3)
Declined participation (n=6)
No time/interest (n=5)
Other health reasons (n=1)
Unable to be reached (n=3)

16 participants agreed to participate and started the experiment

Discontinued participation (n=1)
Unable to perform adequately on task (n=1)

15 participants completed the experiment

Excluded from analysis (n=4)
Contralateral upper body pain at time of experiment (n=1)
No research diagnosis of CRPS at time of experiment, based on screening (n=3)

11 participants were included for analysis of the uncrossed condition (*complete sample*)

Excluded from analysis both conditions (n=2)
|PSS both conditions| > 400 (n=2)

9 participants were included for the analysis of both conditions (*partial sample*)

3. Recruitment of patients with unilateral wrist pain

Recruitment procedure:

Patients with unilateral wrist pain were recruited by Prof. Hollevoet of the Orthopedics Department of the University Hospital Ghent. The doctor addressed supposedly eligible patients during consultation about the study and asked these patients permission to have the experimenter call them. The experimenter called interested patients to give more information about the study and were invited to the hospital to participate in the study.

Inclusion criteria:
- Age 18-70yrs
- Dutch-speaking
- Unilateral wrist pain (duration > 3 months)

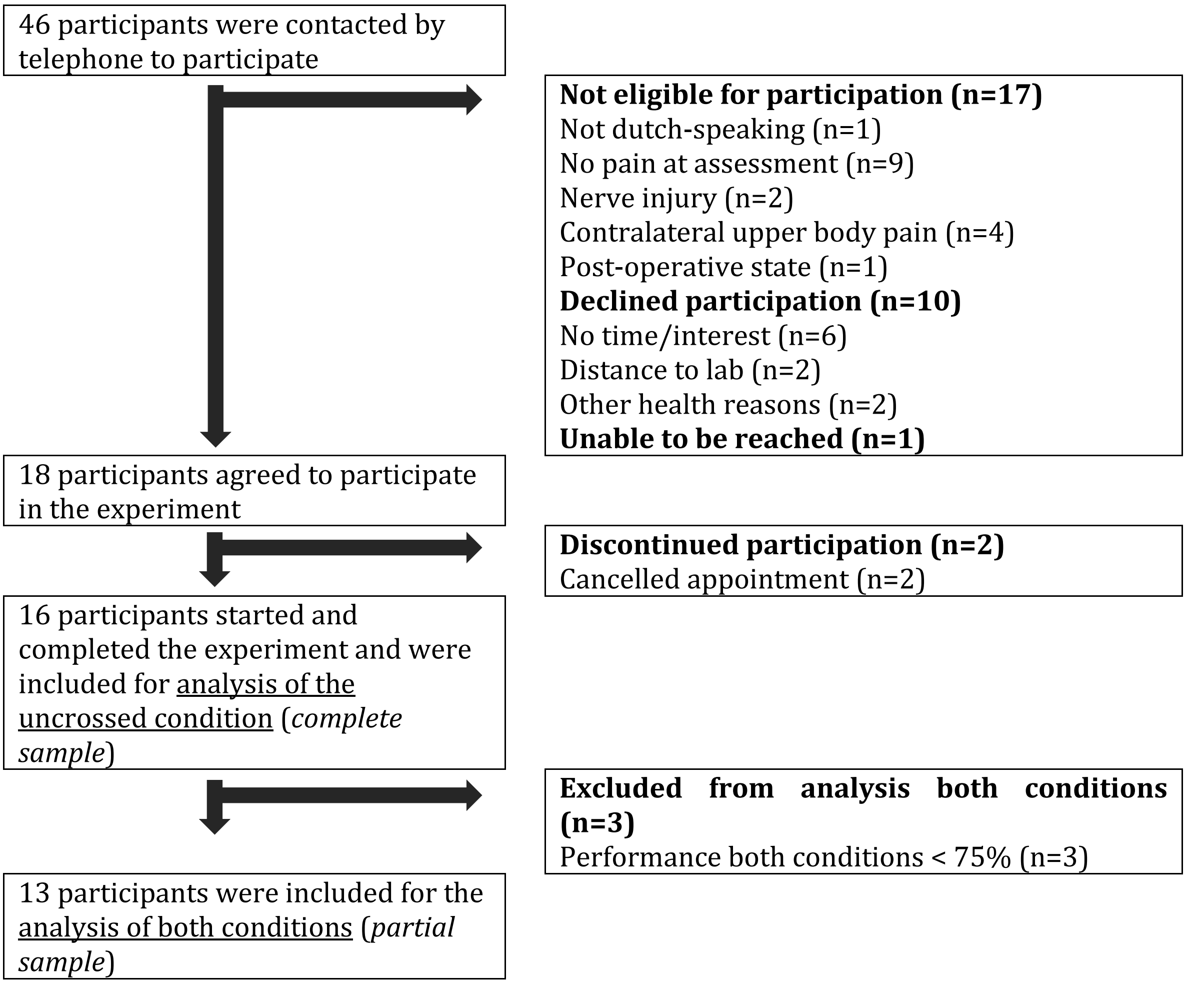
Exclusion criteria:
- Contralateral upper body pain complaints
- Presence of nerve injury or CRPS
- Recent surgery (< 3 weeks) at painful wrist
- Insufficiently corrected visual impairments

Post-experimental exclusion criteria for analysis:
- Contralateral upper body pain complaints at time of experiment
- Presence of research diagnosis of CRPS at time of experiment, based on diagnostic screening

Additional post-experimental exclusion criteria for analysis
- |PSS| uncrossed condition > 400 ⎫ analysis uncrossed condition only
- Performance on trials with highest SOA (200/-200ms) in uncrossed condition < 75% ⎭ (complete sample)

- |PSS| both conditions > 400 ⎫
- Performance on trials with highest SOA (200/-200ms) in both conditions < 75% ⎭ analysis both conditions (partial sample)

Flow-chart recruitment/inclusion unilateral wrist pain patients:



46 participants were contacted by telephone to participate

Not eligible for participation (n=17)
Not dutch-speaking (n=1)
No pain at assessment (n=9)
Nerve injury (n=2)
Contralateral upper body pain (n=4)
Post-operative state (n=1)
Declined participation (n=10)
No time/interest (n=6)
Distance to lab (n=2)
Other health reasons (n=2)
Unable to be reached (n=1)

18 participants agreed to participate in the experiment

Discontinued participation (n=2)
Cancelled appointment (n=2)

16 participants started and completed the experiment and were included for <u>analysis of the uncrossed condition</u> (*complete sample*)

Excluded from analysis both conditions (n=3)
Performance both conditions < 75% (n=3)

13 participants were included for the <u>analysis of both conditions</u> (*partial sample*)

4. Recruitment of patients with unilateral shoulder pain

Recruitment procedure:

Patients with unilateral shoulder pain were recruited by Prof De Wilde and dr. Van Tongel of the Orthopedics Department of the University Hospital Ghent. The doctor addressed supposedly eligible patients during consultation about the study and asked these patients permission to have the experimenter call them. The experimenter called interested patients to give more information about the study and were invited to the hospital to participate in the study.

Inclusion criteria:
- Age 18-70yrs
- Dutch-speaking
- Unilateral shoulder pain (duration > 3 months)

Exclusion criteria:
- Contralateral upper body pain complaints
- Presence of nerve injury or CRPS
- Recent surgery (< 3 weeks) at painful shoulder
- Insufficiently corrected visual impairments

Post-experimental exclusion criteria for analysis:
- Contralateral upper body pain complaints at time of experiment
- Presence of research diagnosis of CRPS at time of experiment, based on diagnostic screening

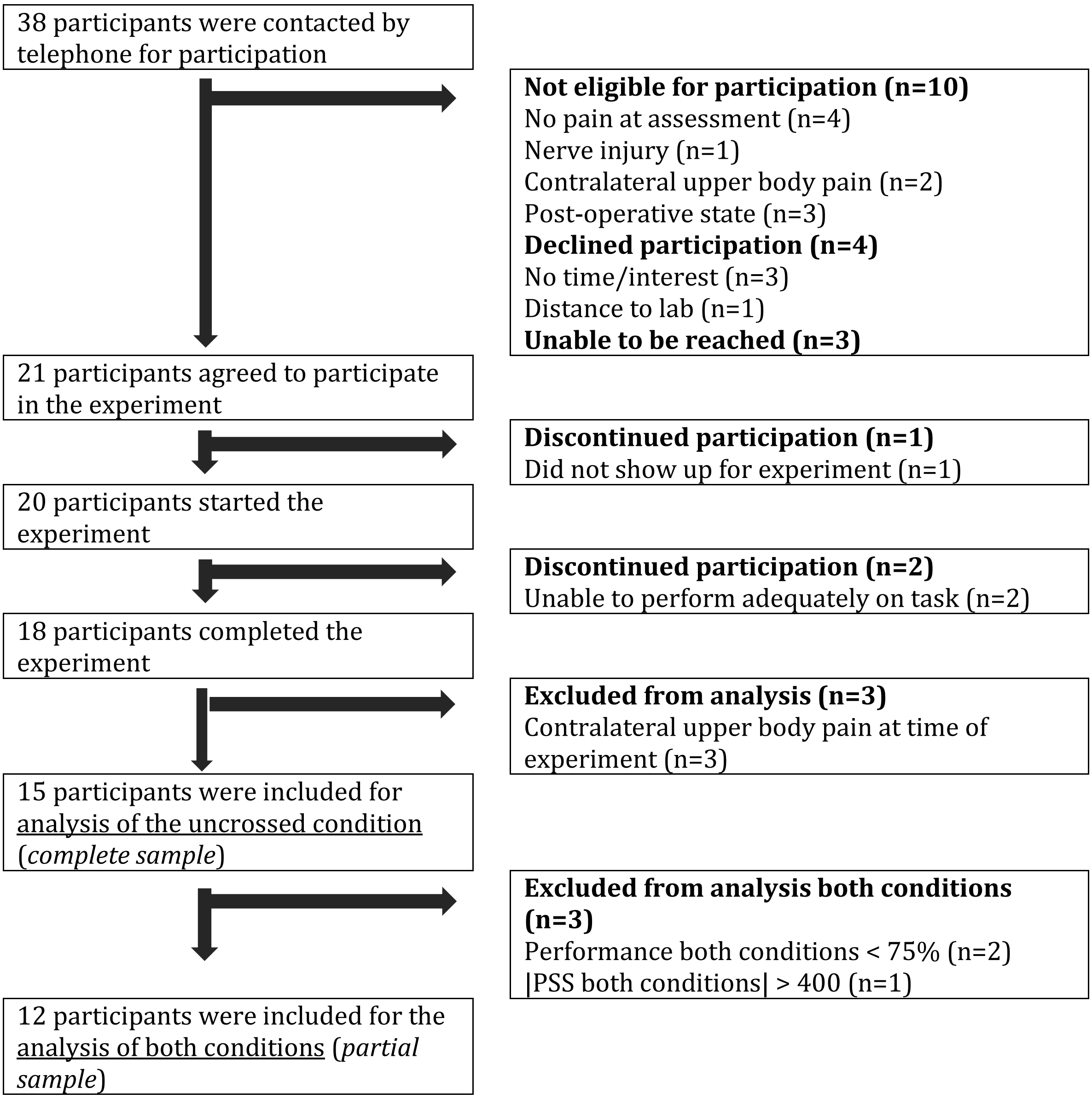
Additional post-experimental exclusion criteria for analysis
- |PSS| uncrossed condition > 400
- Performance on trials with highest SOA (200/-200ms) in uncrossed condition < 75%

analysis uncrossed condition only (complete sample)

- |PSS| both conditions > 400
- Performance on trials with highest SOA (200/-200ms) in both conditions < 75%

analysis both conditions (partial sample)

Flow-chart recruitment/inclusion unilateral shoulder pain patients:



5. Procedure

The procedure was identical for each of the three patient groups and consisted of 3 parts:

- Completion of questionnaires
- Diagnostic screening
- Temporal Order Judgment (TOJ) task

All three parts were completed during one experimental session in the University Hospital Ghent.

5.1. Part 1

In the beginning of the experimental session, participants filled the following battery of questionnaires:

- Anamnestic information (ad hoc developed)
- Items on Coping with Painful Movements (ad hoc developed)
- Pain Grading Scale (Von Korff, Ormel, Keefe, & Dworkin, 1992)
- Hand Dominance Questionnaire (Van Strien, 1992)
- Multidimensional Pain Inventory – part 1 (MPI-part 1; Lousberg et al., 1999)
- McGill Pain Questionnaire (Vanderiet, Adriaensen, Carton, & Vertommen, 1987)
- The Survey of Pain Attitudes (SOPA; Jensen, Karoly, & Huger, 1987)
- Douleur Neuropathique 4 (DN4; Bouhassira et al., 2005)
- State-Trait Anxiety Inventory – Trait Scale (ZBV; Spielberger, 1987)

5.2. Part 2

Each participant underwent a screening procedure to confirm the presence (for CRPS patients) or absence (for unilateral wrist/shoulder patients) of the diagnosis of CRPS. The screening procedure was based on the Budapest Criteria for the research diagnosis of CRPS (Harden, 2010):

1) Continuing pain, disproportionate to any inciting event
2) Must report at least one symptom in all following categories
    a. Sensory: **hyperesthesia** and/or **allodynia**
    b. Vasomotor: reports of **temperature asymmetry** and/or **skin color changes** and/or **skin color asymmetry**
    c. Sudomotor/edema: reports of **edema** and/or **sweating changes** and/or **sweating asymmetry**
    d. Motor/trophic: reports of **decreased range of motion** and/or **motor dysfunction** (weakness, tremor, dystonia) and/or **trophic changes** (hair, nails, skin)
3) Must display at least one sign at time of evaluation on two of more of the following categories:
    a. Sensory: evidence of **hyperalgesia** (to pinprick) and/or **allodynia** (to light touch and/or deep somatic pressure and/or joint movement)

    b. Vasomotor: evidence of **temperature asymmetry** and/or **skin color changes** and/or **skin color asymmetry**
    c. Sudomotor/edema: evidence of **edema** and/or **sweating changes** and/or **sweating asymmetry**
    d. Motor/trophic: evidence of **decreased range of motion** and/or **motor dysfunction** (weakness, tremor, dystonia), and/or **trophic changes** (hair, nails, skin)

4) There is no other diagnosis that better explains the signs and symptoms

- Criteria 1 was assessed by the responsible doctor
- Criteria 2 was assessed by the experimenter interviewing the patient
- Criteria 3 was assessed by the experimenter observing and measuring the patient
- Criteria 4 was assessed by the responsible doctor

The following methods/devices were used on both hands to assess criteria 3 of the diagnosis of CRPS:

- Hyperalgesia: pricking of Semmes-Weinstein filament no. 19 on hands (painfulness on 10-point Likert scale)
- Thermal allodynia: rolling of Rolltemp. Thermorollers on hands (painfulness on 10-point Likert scale)
- Brush allodynia: stroking of brush on hands (painfulness on 10-point Likert scale)
- Temperature asymmetry: temperature assessment of hands with infrared thermometer (°C of left/right hand)
- Skin color changes/asymmetry: picture and observation of hands
- Edema: volumetry indicator (circumference (cm) of hand and wrist)
- Sweating changes/asymmetry: observation of hands
- Range of motion: inclinometer (degrees of dorsal/palmar wrist flexion)
- Motor dysfunction: observation of hands
- Trophic changes: observation of hands

5.3. Part 3

The last part of the study involved performing a temporal order judgment task. The task consisted of three practice blocks and four experimental blocks. After each experimental block, participants filled in a series of items on how they perceived the stimuli and on how they experienced the experiment. Temperature of the hands was also assessed after each block.

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GENERAL DISCUSSION

PREFACE

Detecting, localizing and reacting upon salient stimulus events, such as incoming threats, is crucial in protecting the body from harm (Legrain & Torta, 2015). Although nociceptive stimuli might seem the ideal candidate for the activation of such defensive mechanisms, stimuli from other modalities (e.g. vision, touch, audition) might just as well signal potential danger and become prioritized in processing (Legrain, Iannetti, Plaghki, & Mouraux, 2011). Stimulus events are mostly multimodal in nature (e.g. both visual and tactile) and might be processed in unity. Although evidence is available on crossmodal interactions between vision and touch in the peripersonal space (e.g. Spence, Nicholls, Gillespie, & Driver, 1998), experimental paradigms often lack ecological validity, due to the primary use of static visual stimuli, in contradiction to the dynamic nature of stimulus events in real life. Therefore, one objective was to investigate the effect of approaching visual stimuli on tactile processing in the peripersonal space. Also, less is known about the efficiency of crossmodal interactions in the face of pain or bodily threat, which might, however, be particularly relevant when studying defensive mechanisms, aiming to protect the body. Therefore, another objective was to investigate whether pain anticipation facilitates crossmodal interactions between vision and touch. Finally, investigations of perceptual abilities in CRPS patients have indicated a bias in perceiving tactile stimuli, away from the pathological hand (Moseley, Gallace, & Spence, 2009). However, conflicting results have been reported on the direction of this bias and on its generalizability to other chronic pain populations. Therefore, a final objective was to assess perceptual biases in CRPS patients and in non-CRPS pain controls. In the general discussion that follows, main research findings will be summarized, interpreted and integrated with existing literature and theories. Next, clinical implications and limitations will be discussed and suggestions for future research will be proposed.

MAIN FINDINGS

PART I

In the first part of this PhD thesis, we aimed to investigate crossmodal interactions between vision and touch in a dynamic context, by measuring the effect of approaching visual stimuli on tactile sensitivity.

In **Chapter 1**, we performed a pilot study to assess whether the newly-developed In Vivo Approaching Object (IVAO) paradigm was suitable to measure crossmodal effects of visual approaching stimuli on tactile sensitivity in peripersonal space. One of the participants' hands was approached by a neutral, pen-like object, from nearby or from a further distance. This was followed by a near-threshold tactile stimulus on the same hand (congruent trials), on the opposite hand (incongruent trials), on both hands (bilateral trials), or by no tactile stimulus at all (catch trials). Tactile detection accuracy was calculated as a measure of tactile sensitivity and was expected to be higher for congruent trials than for incongruent trials (= visuo-tactile interaction), especially when the approaching movement was performed near the hands (i.e. in peripersonal space). No evidence was found for our hypotheses, although methodological limitations, such as low power, might have accounted for the lack of significant results.

In **Chapter 2**, the IVAO paradigm was adapted and further developed to investigate visuo-tactile interactions in peripersonal space. The procedure to determine' perceptual thresholds was improved, the standardization of the visual approaching movement was improved, and the power was increased by changing the number and proportion of trials. In Experiment 1, participants were again visually approached towards to left or right hand, but only close to the hands (i.e. in peripersonal space). This was followed by a near-threshold tactile stimulus on the same hand (congruent trials), on the opposite hand (incongruent trials), or on both hands (bilateral trials) or by no tactile stimulus at all (catch trials). In Experiment 2, a condition was added in which the approaching movement took place at a further distance from the hands (i.e. in extrapersonal space). According to expectations, tactile sensitivity was higher on the approached hand than on the opposite hand (congruent > incongruent), especially when the approaching movement was near the hands, in peripersonal space. As such, these studies provided evidence on crossmodal interactions between vision and touch in peripersonal space, by using a paradigm that accounts for the dynamic nature of stimuli in real life.

In **Chapter 3**, the IVAO paradigm was adapted to provide more insight into the role of vision, independent of proprioception, in crossmodal interactions between vision and touch. Participants hands were now hidden from sight while they were approached, and in one condition, rubber hands were placed realistically in front of participants to create the illusion that this were the real hands. Near-threshold tactile stimuli were administered on the approached hand (congruent trials), the opposite hand (incongruent trials), or on both hands (bilateral trials), or no tactile stimulus was provided (catch trials). Tactile detection accuracy was compared between congruent and incongruent trials and between trials in which rubber hands were present versus absent. Accuracy was expected to be higher in congruent trials, especially when rubber hands were present. Moreover, we expected the effect of the rubber hands to be modulated by the degree of embodiment with the rubber hands. Results indicated that tactile sensitivity was higher when rubber hands were present, irrespective of visual cueing effects. Moreover and as expected, tactile sensitivity was higher for the approached hand than for the opposite hand (congruent > incongruent), especially when the rubber hands were present. The effect of embodiment was unclear. This study suggested that, although information about the position of the approached body-parts (i.e. proprioception) might be sufficient to install a crossmodal effect on tactile processing, vision of approached body-parts further enhances these crossmodal interactions.

PART II

In the second part of this PhD thesis, we aimed to investigate crossmodal interactions between vision and touch during the anticipation of pain.

In **Chapter 4**, the IVAO paradigm was adapted to investigate the effect of approaching visual stimuli on tactile processing when the approaching movement signals imminent pain. Participants' hands were approached by a pen in one of two colors (blue or yellow) of which one color signaled the possible occurrence of a painful stimulus on the approached hand (pain signal), and the other color signals the absence of pain (safety signal). Approaching movements were followed by a near-threshold tactile stimulus on the approached hand (congruent trials), the opposite hand (incongruent trials), or on both hands (bilateral trials), or by no tactile stimulus at all (catch trials). Tactile detection accuracy was compared between congruent and incongruent trials and between trials in which pain was signaled and trials in which no pain (safety) was signaled. As hypothesized, tactile sensitivity was higher on the approached hand than on the opposite hand (congruent > incongruent), although less explicitly than expected. In contrast, pain anticipation did not facilitate visuo-tactile interactions, but diminished overall detection accuracy, especially on the approached hand. Several factors were discussed that might account for the interruptive effect of pain anticipation found in this study.

In **Chapter 5**, the temporal order judgment (TOJ) task was used to investigate visuo-tactile interactions in peripersonal space when one part of the body is threatened by imminent pain. Participants judged the temporal order of pairs of vibrotactile stimuli, one applied to either hand. This was preceded by the presentation of a visual cue on the same side (congruent trials), the opposite side (incongruent trials) or on both sides (bilateral trials), and either near the hands (i.e. in peripersonal space) or far from the hands (i.e. in extrapersonal space). In addition, participants were instructed that they might receive a painful stimulus on one of their hands. The point of subjective simultaneity (PSS) was calculated to assess perceptual biases towards or away from the cued side, both in peri- and extrapersonal space, and towards or away from the pain-threatened side. As expected, a perceptual bias was found towards the cued side in peripersonal space, but not in extrapersonal space. Pain anticipation did not facilitate visuo-tactile interactions in peripersonal space, nor in extrapersonal space. In contrast, the results suggested a perceptual bias away from the pain-threatened hand. Several theoretical assumptions are discussed that might explain the unexpected effect of pain pain-induced bodily threat.

PART III

In the second part of this PhD thesis, we aimed to investigate the perception of touch in patients with Complex Regional Pain Syndrome (CRPS), compared to patients with non-CRPS chronic pain.

In **Chapter 6**, we used a TOJ task to replicate the findings of Moseley et al. (2009) on perceptual biases in CRPS patients and to extend them by also testing two groups of non-CRPS pain controls: a group of unilateral wrist pain patients and a group of unilateral shoulder pain patients. All participants judged the temporal order of pairs of vibrotactile stimuli, one applied to either hand. Judgments were made with arms in a normal, uncrossed position or with the arms crossed over the body midsagittal plane. Based on Moseley et al. (2009), we expected to find a perceptual bias away from the pathological hand when arms were uncrossed, and a bias towards the pathological hand when arms were crossed. In the pain controls, we expected a bias towards the painful hand, irrespective of the position of the arms. We were not able to replicate the results of Moseley et al. (2009) and found no clear evidence for any perceptual biases in the non-CRPS pain controls. However, individual differences were large and suggest that other variables (e.g. pain intensity and duration) might have played a role.

THEORETICAL IMPLICATIONS

The aim of this PhD thesis was to investigate spatial perception processes, primarily crossmodal interactions, under several circumstances, namely: in a dynamic environment, during pain anticipation, and in chronic pain patients, including CRPS patients. First, evidence of crossmodal interactions between vision and touch in the peripersonal space is summarized, with specific attention to the dynamic nature of stimuli and the respective roles of vision and proprioception in visuo-tactile interactions. Next, the impact of pain anticipation on visuo-tactile interactions is reviewed theoretically. Following this, a theoretical discussion is provided on the underlying mechanisms of the visuo-tactile interactions observed in this PhD. Finally, the findings on the perception of touch in CRPS and non-CRPS chronic pain patients are discussed critically.

VISUO-TACTILE INTERACTIONS IN THE PERIPERSONAL SPACE: A DYNAMIC APPROACH

As already discussed in the general introduction of this PhD thesis, when perceiving the world, information from multiple sensory modalities is provided all at once. To create a more accurate and coherent representation of this world and of potentially relevant or threatening events in it, the brain integrates stimuli that reach our different senses (Spence & Driver, 2004). Such crossmodal interactions have been well-reported for most combinations of sensory modalities (see Driver & Spence, 1998), but of particular relevance is the interaction between stimuli on the body (e.g. tactile) and stimuli in the external space (e.g. visual stimuli). Although evidence has already been found for crossmodal interactions between vision and touch (e.g. Spence et al., 1998), experimental paradigms reporting this often lack ecological validity. Due to the primary use of static visual stimuli in human studies, experiments have not resembled the complex and dynamic nature of real-life situations. Therefore, we developed the In Vivo Approaching Object (IVAO) paradigm that includes actual moving visual stimuli, approaching the participant's body, followed by near-threshold vibrotactile stimuli on the body. We investigated whether approaching the body with a neutral object increases tactile sensitivity on the approached body-part.

In Chapter 2, we found that watching being approached increased tactile sensitivity on the approached body-part. Moreover, we found in a second study that this visuo-tactile interaction only existed when participants were approached from nearby the body (i.e. in peripersonal space), but not from a further distance (i.e. in extrapersonal space). As such, these results provided direct evidence for a crossmodal link between vision and touch in peripersonal space, in line with earlier crossmodal studies (e.g. Spence et al., 1998). Moreover, according to our knowledge, this was the first study to find evidence for visuo-tactile interactions in peripersonal space in humans by using in vivo approaching stimuli, thereby maximally preserving ecological validity.

THE ROLE OF VISION AND PROPRIOCEPTION

The fact that visuo-tactile interactions, as found in Chapter 2 of this PhD, mainly occur close to the body implies that the brain somehow tracks the proximity of stimuli in external space (e.g. approaching objects) with respect to the body. However, it remains unclear whether the perception of the spatial proximity between visual and tactile stimuli is purely driven by vision (i.e. *seeing* your body-parts near the visual stimulus) or whether it is modulated by proprioception (*feeling* your body-parts on that location). Therefore, in Chapter 3, we aimed to gain more insight into the contribution of vision, irrespective of proprioception, in visuo-tactile interactions. We occluded participants' hands from vision to investigate whether approaching the unseen hands can already elicit increased tactile sensitivity on the approached hand, based on proprioceptive knowledge solely. Moreover, we used the rubber hands illusion to test whether vision of rubber hands, aligned realistically, increases tactile sensitivity on the approached (real) hand. Based on previous studies, we expected the effect of the rubber hands to be modulated by feelings of embodiment (e.g. ownership) towards the artificial hands. We found that approaching participants' body increased tactile sensitivity on the hand, corresponding to the approached side of space, but especially when rubber hands were approached. As such, proprioceptive information alone was sufficient to elicit increases in tactile sensitivity on the approached body-parts, but visual information (i.e. seeing hands being approached) further increased tactile sensitivity.

In that respect, the results of Chapter 3 suggest an additive effect of vision over proprioception in crossmodal interactions between vision and touch, which is in line with several other studies (e.g. Làdavas, Farnè, Zeloni, & di Pellegrino, 2000; Pavani, Spence, & Driver, 2000; Wesslein et al., 2014). For example, Làdavas et al. (2000) found that tactile perception was enhanced when the hands were visible during the presentation of visual stimuli (vision + proprioception), as opposed to when hands were invisible (only proprioception). This so-called dominance of vision over proprioception has been explained in relation to the existence of bimodal visuo-tactile neurons in the macaque cortex, of which the activity in response to visual stimuli near the hand is reduced or even extinguished when vision of the stimulated hand is prevented (Làdavas et al., 2000). However, more research is still needed to gain better insight into the brain mechanisms underlying visuo-tactile interactions in humans.

In the rubber hand illusion study by Pavani et al. (2000), visuo-tactile interactions were less apparent when rubber hands were aligned unrealistically, suggesting that the incorporation of the rubber hands into the body representation was a necessary prerequisite. Indeed, it was found in a similar study (Wesslein et al., 2014) that embodiment with the rubber hands modulated the enhancement of tactile perception, an element that we were not able to replicate in such an explicit manner. Body ownership, as a subcategory of embodiment, did seem to modulate our results, but only in some of the conditions (i.e. in trials with targets of supra-threshold intensity). A more extensive set of items assessing all subcategories of embodiment, according to a psychometric analysis (Longo, Schüür, Kammers, Tsakiris, & Haggard, 2008), namely *Ownership* (i.e. the feeling that the rubber hands are part of one's own body), *Location* (i.e. the feeling that the rubber hands and one's own hands are in the same place and referring to sensations of causation between seen and felt touches), and *Agency* (i.e. the feeling of being able to move the rubber hands and of having control over it*)* might have provided more information on the role of embodiment in the current results. Also, although we did not conduct a follow-up experiment in which the rubber hands were also aligned unrealistically, we assume to have found similar results as in the study of Pavani et al. (2000).

VISUO-TACTILE INTERACTIONS DURING PAIN ANTICIPATION

An important function of spatial perception is to detect and localize stimuli that might threaten the body's integrity. Those stimuli can originate from any modality, as long as they are capable of attracting attention by standing out against other stimuli (e.g. suddenly being stung by a wasp) or fit within current cognitive goals or mindsets (e.g. watching out for the sound of wasps during a summer picnic). Moreover, it was shown that the brain is especially susceptible to stimuli approaching the body (cf. Chapter 2), as they tend to predict something impacting on the body. For example, it was found that the perception of stimuli on the body is dependent on people's judgments about the time and location of impact of a visual stimulus (Kandula, Hofman, & Dijkerman, 2015).

Besides these situations, other contextual factors might also affect spatial perception, such as the threat of experiencing painful sensations. Much research has been conducted on the effect of bodily threat on spatial perception, especially by presenting participants with pictures depicting threatening objects (e.g. a spider) (e.g. Lloyd, Morrison, & Roberts, 2006; Öhman, Flykt, & Esteves, 2001; Van Damme, Gallace, Spence, Crombez, & Moseley, 2009). Although clear evidence has been found for the facilitation of perceiving stimuli on or near the threatened body-part, in the same but also in other modalities (e.g. Poliakoff, Miles, Li, & Blanchette, 2007; Van Damme et al., 2009), threatening pictures pose no real threat to the body. Therefore, it might be advantageous to investigate the effect of anticipating actual pain on spatial perception. Some studies have shown increased tactile perception on body-parts that were threatened by pain (Van Damme, Vanden Bulcke, Durnez, & Crombez, 2016; Van Hulle, Durnez, Crombez, & Van Damme, 2015; Vanden Bulcke, Crombez, Durnez, & Van Damme, 2015; Vanden Bulcke, Van Damme, Durnez, & Crombez, 2013), but no clear evidence is available for the effect of pain anticipation on crossmodal interactions near the body. Given that the peripersonal space has been described as a defensive safety-margin surrounding the body, characteristic of visuo-tactile interactions, we hypothesized that being threatened by pain would facilitate crossmodal interactions between vision and touch in the peripersonal space.

First of all, the results of Chapter 4 and 5 corroborated the findings of Chapter 2 and 3 on visuo-tactile interactions near the body. Approaching a body-part (Chapter 4) or presenting a visual cue near a body-part (Chapter 5) increased tactile processing on the cued body-part, regardless of pain anticipation. However, visuo-tactile interactions were less strong than in the previous chapters, especially during pain anticipation. Indeed, opposite to our expectations, we observed in Chapter 4 that pain anticipation diminished the detection of tactile stimuli overall, but especially on the approached body-part. This indicates that visuo-tactile interactions were less strong on the side on which pain was anticipated. Similarly, in Chapter 5, somatosensory perception was shifted towards the visually cued side (= visuo-tactile interaction), but only when that side was *not* threatened by pain. As such, the results of both studies seem to indicate that pain anticipation disrupted visuo-tactile interactions on the threatened body-part.

These results are not in agreement with former studies on bodily threat, in which it was generally found that the detection of tactile stimuli is increased on the threatened body-part (Poliakoff et al., 2007; Van Damme et al., 2009). However, in these studies, threatening pictures near the hands were used to induce threat, as opposed to the pain stimuli used in our studies. There have been studies in which the effect of pain anticipation on perception was measured, but only within a single modality (e.g. Koster et al., 2004; Vanden Bulcke et al., 2013). On the other hand, there are some studies reporting lower task performance during pain anticipation (Dawson, Schell, Beers, & Kelly, 1982; Lipp, Siddle, & Dall, 1993), or even attentional shifts away from a painful body-part (e.g. Moseley et al., 2009). For example, in patients with complex regional pain syndrome, shifts in tactile perception *away* from the painful hand were observed. Although we should remain cautious in generalizing observations from chronic pain populations to healthy populations, the latter findings suggest that attentional biases towards bodily threat are not *per se* hard-wired, but might depend on several contextual factors.

A likely possibility is that the threat of having pain demanded so much attentional resources that this diminished the effect of visual cues on tactile processing. For example, de Haan (2016) has argued that difficulty disengaging from threatening visual stimuli might delay attention to shift towards other (task-relevant) stimuli. Difficulty disengaging from the pain signaling approaching movement in Chapter 4 might then have impeded the detection of tactile targets on the approached side, as evidenced by weaker visuo-tactile interactions. Yet, as the visual stimuli in Chapter 5 (LEDs) did not signal pain (i.e. this was signaled by verbal instructions at the beginning of each block) and thus could not have been perceived as threatening, the latter explanation cannot fully account for the given results. Conversely, another explanation presumes that people might 'break away from aversive stimuli' (Sokolov, 1963, p. 14), resulting in diminished information processing. According to Sokolov (1963), stimuli of low or moderate intensity evoke an orienting reflex that facilitates the discrimination of sensory input, whereas stimuli of high intensity (e.g. aversive or painful stimuli) elicit a defensive reflex that inhibits orienting and facilitates defensive movements. Although participants were not allowed to make (defensive) movements during our studies, the existence of such a defensive reflex could have impeded the processing of sensory input at the threatened body-part. Furthermore, cognitive factors, such as fear or worrying about receiving painful stimuli, could have diminished overall task performance, as suggested by several studies (Öhman, 1979; Sarason, Pierce, & Sarason, 2014).

Evidently, more research would be needed to further investigate the unexpected effect of pain anticipation on crossmodal interactions between vision and touch in healthy participants, but also in chronic pain patients. Future studies should also investigate whether the inhibitory effect of pain anticipation on visuo-tactile interactions is specific for the anticipation of pain, or depends on the anticipation of a sensory event *an sich*, for example by including a control condition in which a non-painful somatosensory stimulus is anticipated.

VISUO-TACTILE INTERACTIONS IN THE PERIPERSONAL SPACE: CROSSMODAL SPATIAL ATTENTION OR MULTISENSORY INTEGRATION?

Based on these studies, it remains uncertain which mechanisms underlie crossmodal interactions between vision and touch in peripersonal space. From within cognitive psychology, crossmodal cueing effects have generally been ascribed to (covert) crossmodal spatial attention (Spence & Driver, 2004). *Crossmodal spatial attention*, described as the ability to orient attention towards a common external source across several modalities (Spence, 2010; Spence & Driver, 2004), implies that a stimulus in one modality attracts attention to all other stimuli that are present on that location. This would be controlled by a supra-modal system in the brain that coordinates attention to one location, regardless of stimulus modality (Eimer & Driver, 2001). However, an alternative explanation is provided for interpreting the results. *Multisensory integration* assumes that crossmodal interactions are caused by stimulus-driven integration of multisensory inputs, controlled by modality-specific mechanisms that spread to other sensory modalities (Spence & Driver, 2004). Related to this is the discovery of bimodal neurons, found in the ventral premotor cortex and ventral intraparietal sulcus of the monkey brain (Duhamel, Colby, & Goldberg, 1998; Graziano, Yap, & Gross, 1994; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981a, 1981b). These neurons have both visual and tactile receptive fields that are in approximate spatial register to each other. As such, when a visual stimulus is present, nearby a tactile stimulus on the body, these neurons are activated and visuo-tactile processing is enhanced, even during movement of the respective body-part. Although evidence for bimodal neurons has only been found in the monkey brain, similar mechanisms might take place in humans as well.

Discriminating between crossmodal spatial attention and multisensory integration in explaining crossmodal interactions has proven difficult. However, taking a closer look towards the relative timing of the stimuli (i.e. cue and target) in the different modalities might shed some light on the difference between crossmodal spatial attention and multisensory integration. It seems fairly straightforward that stimuli that occur close in time or even in simultaneity would cause maximal multisensory integration, as such stimuli tend to reflect a common external event. Even though evidence was found for this assumption (Bolognini, Frassinetti, Serino, & Làdavas, 2005), two issues impede us to discriminate between both accounts, solely based on the relative timing of the stimuli. First, multisensory interactions, caused by bimodal neurons in monkeys, can arise even with CTOAs up until 600ms (Meredith, Nemitz, & Stein, 1987). Second, simultaneity between cue and target should not simply be considered based on the relative timing of stimulus presentation, but also on the relative timing of arrival times of sensory inputs from each modality at various multimodal integration sites in the brain (Spence & Squire, 2003). These arrival times will depend on the brain areas that are involved, but also on the stimuli that are used (e.g. sounds arriving later than lights from a certain distance). As such, the concept of simultaneity is complex and might not provide sufficient evidence to discriminate between both explanations. On the other hand, even though the distinction between crossmodal spatial attention and multisensory integration might seem merely semantic at first sight, distinct neural mechanisms are believed to be involved. As a result, behavioral measures do not suffice to separate these two accounts. More specialized research, such as combined ERP and fMRI measures, lesions studies, or TMS studies are needed to gain more insight into the underlying mechanisms, in humans, of visuo-tactile interactions in the peripersonal space.

EXOGENOUS VERUS ENDOGENOUS CUEING EFFECTS IN THE IVAO AND THE TOJ PARADIGM

Apart from the possibility of multisensory integration mechanisms in the human brain, we might expect that our results are, at least in part, explained by attentional processes. However, a further distinction needs to be made between exogenous or stimulus-driven spatial attention and endogenous or goal-driven spatial attention, whereby in the first case, attention is captured by abrupt and uninformative stimuli, and in the latter case, stimuli are attended selectively, due to their relevance for ongoing cognitive goals or actions (Driver & Spence, 1998).

Although we assumed to measure shifts in exogenous spatial attention by using the IVAO paradigm, this assumption seems debatable. On the one hand, the direction of the approaching movements in the IVAO paradigm was always lateralized, which is characteristic for exogenous spatial cueing paradigms. Moreover, participants were never instructed to attend one location of space in a certain modality, which is usually the case in endogenous paradigms. On the other hand, certain issues question the exogenous nature of the in vivo approaching movement. First, the arousing quality of the approaching movement was less explicit than visual cues in other exogenous crossmodal attention experiments (e.g. De Paepe, Crombez, Spence, & Legrain, 2014; Spence et al., 1998). It's onset was less abrupt than, for example, a flash of light emitted by a LED (cf. Chapter 5) or a burst of noise. Also, as the approaching movement was present in every trial throughout an experiment, it was not infrequent and therefore not novel. Second, although the approaching movement was, strictly spoken, uninformative about the location of tactile targets, it might have installed some expectations about receiving a tactile stimulus on the approached hand (i.e. due to the duration of the approaching movement, participants could covertly watch the pen moving towards the left or right hand; e.g. see Colon, Legrain, Huang, & Mouraux, 2015), or this expectation might have been present by default, as a visuo-tactile predictive mechanism or due to past learning experiences (e.g. see Kandula, Hofman, & Dijkerman, 2015). Third, although the effect of pain anticipation was opposite to expectations in Chapter 4, different outcomes after being approached by the blue versus the yellow pen, indicates that pen color – and especially what the color signals, namely pain versus safety – was consciously interpreted and therefore processed as a symbolic (endogenous cue). In this respect, endogenous spatial attention would have been manipulated, or at least a combination of both types of spatial attention.

A few more characteristics of the effects of cues can be reviewed to distinguish between exogenous and endogenous attention effects. One distinction concerns the extent of the facilitative effect of the cues, depending on the cue validity, that is, the percentage of trials on which the expected target will appear at a cued location (i.e. congruent trials). While the facilitative effect might be similar for exogenous and endogenous cues when cue validity is high, it is expected to decrease for endogenous cues, but not for exogenous cues, when cue validity decreases (see Wright & Ward, 2008). It is then presumed that, when participants learn, over the course of an experiment, that a cue does not reliably predict the location of a subsequent target, it is no longer regarded as useful and no longer voluntarily attended, hence the decrease in facilitative effects for endogenous cues. In contrast, exogenous cues would maintain to facilitate the localization of targets, due to their reflexive/stimulus-driven nature, even when they are no longer consciously used to predict the target location. Although cue validity was not manipulated in the IVAO experiments in this PhD, facilitative effects of visual cues (i.e. visuo-tactile interactions) did not diminish throughout the course of the experiment, notwithstanding the fact that cues did not reliably predict target location. this suggests that visual cues were processed in a stimulus-driven, exogenous manner. Another distinction is related to the time course of facilitative effects of endogenous versus exogenous cues. Whereas effects of exogenous cues usually appear at smaller cue-target onset asynchronies (CTOAs), for example 100ms, and quickly diminish after that, effects of endogenous cues typically appear at larger CTOAs (e.g. 300ms) and are sustained for a longer period (e.g. up until 2 seconds; e.g. see Müller & Rabbitt, 1989; Shepherd & Müller, 1989). In our case, the delay between the tapping of the pen and tactile stimulus delivery was virtually zero, except a small interval of ~2ms due to the technical composition of the apparatus. However, as the visual cues were dynamic, there was no distinct time point of cue presentation, which makes it impossible to calculate CTOAs. Nevertheless, as the approaching movement took at least 1000ms, the time course between stimulus onset of the visual cue and that of the tactile target seems incompatible with exogenous spatial attention effects. Follow-up studies would be needed to ascertain whether exogenous or endogenous mechanisms were responsible for the effect of approaching the body on tactile sensitivity. For example, cue validity could be manipulated to investigate whether the cueing effects diminish when cue validity decreases. In addition, the effect of competing attentional demands, caused by a secondary, cognitive-load task (e.g. memorizing digits) might shed light on the exogenous-endogenous distinction, as endogenous cueing effects are diminished when a secondary task demands attention, whereas exogenous cueing effects remain stable (Schneider, Dumais, & Shiffrin, 1984). Finally, participants could be instructed to ignore the approaching movement, as it was found that exogenous cueing effects are not affected by instructions to ignore the cues, whereas endogenous cueing effects tend to diminish after this instruction (Wright & Ward, 2008).

In the TOJ study measuring visuo-tactile interactions (Chapter 5), evidence can be found for both exogenous and endogenous components. Visual stimuli (LEDs) were bright, sudden, and non-predictive of the location of subsequent tactile targets. Moreover, visuo-tactile interactions occurred with CTOAs of 20ms, also indicating exogenous cueing processes. In addition, visuo-tactile interactions did not diminish throughout the experiment, despite a rather low cue validity (30%). On the other hand, participants were instructed that a painful stimulus might be administered on one hand, possibly causing them to selectively attend one side of space, which is a typical feature of endogenous cueing paradigms. Therefore, we presume that both exogenous and endogenous processes can explain the effect of visual stimuli (light flashes) on the temporal perception of touch during anticipation of pain.

THE PERCEPTION OF TOUCH IN COMPLEX REGIONAL PAIN SYNDROME

During the last decades, pain researchers have grown increasing interest in the study of complex regional pain syndrome (CRPS), due to its complex symptomatology, including sensory, motor and vegetative symptoms, but also deficits in spatial perception, such as impaired body representations and biases in somatosensory perception. For example, Moseley et al. (2009) found that CRPS patients tend to bias the temporal perception of tactile stimuli on the hands, in favor of the non-pathological hand, and to the detriment of the pathological hand, resembling post-stroke hemi-spatial neglect (e.g. Hasselbach & Butter, 1997). Remarkably, when patients' hands were crossed over the body midsagittal plane, the bias was completely reversed, that is, patients now displayed a bias *towards* the pathological hand, which indicates that the somatosensory bias is not anchored to the pathological hand (i.e. dependent on a somatotopic representation of the body), but to the region of space where the pathological hand normally resides (i.e. dependent on a spatiotopic representation, taking into account the position of the limbs in space). Although these findings indicate a bias *away from* the pathological hand, when arms are in a normal, uncrossed position, other studies have observed opposite effects (Sumitani, Rossetti, et al., 2007; Sumitani, Shibata, et al., 2007; Uematsu et al., 2009). For example, Sumitani et al. (2007) observed a bias *towards* the pathological hand in a visual subjective body midline test when it was performed in the dark, which was reduced during a nerve block by a lidocaine injection (Sumitani, Shibata, et al., 2007). In contrast to the findings of Moseley et al. (2009) reflecting a neglect-like perceptual bias, the latter studies suggest a somatosensory bias *towards* the pathological hand, possibly resulting from excessive information coming from the affected hand. Clearly, conflicting findings exist on the direction of biases in spatial perception in CRPS patients (see Legrain, Bultitude, De Paepe, & Rossetti, 2012 for an overview). Moreover, it remains unclear to what extent these symptoms can be generalized to other chronic pain populations (e.g. see Kolb, Lang, Seifert, & Maihöfner, 2012). Therefore, we investigated, based on the study of Moseley et al. (2009), the perception of touch during an uncrossed or crossed arm position, in a group of CRPS patients, and in two groups of chronic unilateral pain controls, namely chronic wrist pain and chronic shoulder pain.

Based on the results from the study in Chapter 6, we were not yet able to answer the research questions listed above. We did not find a consistent somatosensory bias, towards or away from the CRPS affected hand in the CRPS group, nor did we find such bias in the pain control groups (in either arm position). However, individual variability was quite large, leading us to believe that other factors might be involved, such as pain intensity or pain duration. For example, it was recently shown that body perception in CRPS patients was related to pain intensity

(Schwoebel, Coslett, Bradt, Friedman, & Dileo, 2002; Schwoebel, Friedman, Duda, & Coslett, 2001) and pain duration (Förderreuther, Sailer, & Straube, 2004). Although we did find some evidence for the role of these variables, power was too low to draw definite conclusions. Therefore, future studies are clearly needed to reconcile the conflicting findings on the perception of touch in CRPS and to assess the generalizability of these symptoms to other chronic pain populations.

CLINICAL IMPLICATIONS

According to the results of Chapter 2, approaching a person with a neutral object increases tactile sensitivity on the approached body-part. This might also be relevant in a clinical context, in which patients are often approached by doctors during clinical examinations. The patient, watching the doctor approaching him/her, would then be confronted with not only somatosensory information (i.e. the doctor touching the patient with a medical device or the hands), but also with visual information (i.e. the doctor approaching the body). For example, when confirming the diagnosis of CRPS (Harden et al., 2010) or when performing quantitative sensory testing (QST), patients are approached and touched in order to determine the presence of sensory symptoms, such as hyper- or hypoesthesia or allodynia to light touch (Harden, 2010). In those cases, clinicians/researchers assume that the results of such sensory tests reflect the functional states of somatosensory systems. However, given our results, we imagine that such somatosensory evaluations might be biased because of the doctor approaching the patient (cf. visuo-tactile interactions). More specifically, the presence or magnitude of sensory symptoms could be overestimated, due to increased tactile sensitivity on the approached body-part.

Evidently, we should be careful not to over-interpret our findings concerning its clinical implications. First of all, we have no indication yet on the size of the increased tactile sensitivity, following visual approaching movements. Therefore, we cannot conclude that approaching a patient would lead to the misinterpretation of sensory testing data (e.g. QST) or even to actual misdiagnosis – e.g. in CRPS patients, where the diagnosis is dependent on the presence of a certain number of sensory symptoms. To determine the size of enhanced tactile sensitivity following visual approach, other outcome variables are necessary, measuring the perceived intensity of the tactile stimuli on a numerical scale. Second, one might wonder whether approaching patients would also increase their pain sensitivity. A recent study suggested this might be the case, illustrated by faster detection of nociceptive stimuli on the hands when visual stimuli – visible but not overtly watched by the participant – approached the body, as opposed to when they receded from the body (De Paepe, Crombez, & Legrain, 2016). However, in this study, reaction times were measured, which gives no indication of higher intensity ratings of nociceptive stimuli. Furthermore, given that patients probably also watch the body-part that is approached and touched by the doctor, research has indicated antagonistic effects for pain and touch during vision of the body. Watching the body was found to increase tactile sensitivity (cf. Visual Enhancement of Touch [VET] effect; e.g. Kennett et al., 2001), but to decrease perceived pain (cf. visual analgesia; e.g. Longo, Betti, Aglioti, & Haggard, 2009), although in different types of paradigms. As of yet, no study has investigated the effect of approaching visual stimuli on the perception of nociceptive stimuli, while overtly watching the body. Third, as we only investigated healthy participants with the IVAO paradigm, it remains uncertain whether similar effects would occur when approaching a patient with chronic pain (e.g. see Moseley, Sim, Henry, & Souvlis, 2005). For instance, chronic pain is believed to be associated with long-lasting cortical reorganization, compared to acute pain (Seifert & Maihöfner, 2011). In addition, several top-down variables might also play a more explicit role in chronic pain patients. For example, fibromyalgia patients tend to display an over-attentiveness towards sensory stimuli (Crombez, Van Damme, & Eccleston, 2005; McDermid, Rollman, & McCain, 1996), which could increase the effect of approaching and touching the body. Also, chronic patients might anticipate pain to a larger extent than healthy participants when being approached towards a painful body-part, due to past negative experiences. Although the study in Chapter 4 suggested less effect of approaching someone on tactile sensitivity during the anticipation of pain, these results are still under discussion and need further replication. In conclusion, we suggest that until new studies have provided more insight into the role of watching being approached on tactile and pain perception in a clinical context, doctors could instruct patients to close their eyes during somatosensory evaluations to eliminate the effect of visual input on somatosensory perception.

Spatial perception processes, such as crossmodal interactions, might not only affect diagnostic procedures, but its close relationship with pain has also provided intriguing new insights for the development of rehabilitation techniques for chronic pain. Especially relevant to that respect is the rehabilitation of CRPS. Whereas before, clinicians attributed immobility and disuse of the CRPS affected hand to negative consequences (e.g. pain or failure to move) following earlier attempts to use the affected hand (i.e. *learned-nonuse theory*; Schürmann, Gradl, Andress, Fürst, & Schildberg, 1999; Woolf, Shortland, & Sivilotti, 1994), researchers now believe that pain might be a consequence, rather than a cause, of the pathologies underlying CRPS (e.g. see Bultitude & Rafal, 2010). For example, according to the *remapping theory* (Ramachandran & Hirstein, 1998), pain in CRPS patients might result from the absence of sensory (e.g. proprioceptive) feedback when attempting to move the motor impaired limb, causing cortical reorganization in the primary somatosensory cortex (Maihöfner, Handwerker, Neundörfer, & Birklein, 2003; McCabe, Haigh, Halligan, & Blake, 2003). Moreover, absent or modified feedback after motor attempts has been also been linked to a cortical reorganization of the 'body map' in the primary somatosensory and motor cortices (S1 and M1; Maihöfner et al., 2003; Maihöfner, Handwerker, Neundörfer, & Birklein, 2004). Although the underlying pathophysiology is still uncertain, recent theories seem to share the idea of a mismatch between motor control and proprioceptive and visual feedback during movement initiation. Based on these assumptions, rehabilitation techniques have been developed that aim to solve this mismatch by remapping the primary somatosensory cortex through visual illusions. More specifically, it was found that CRPS patients can be treated with mirror box therapy, which was first developed to manage phantom limb pain in amputees (Ramachandran, Rogers-Ramachandran, & Cobb, 1995). In the mirror box illusion, patients watch the mirror reflection of their unaffected limb during simultaneous movement of both the affected and unaffected limb (attempted motor commands in amputees), thereby creating the illusion that the affected limb is moving 'effortlessly' (Ramachandran & Hirstein, 1998). According to several studies, repeated exposure to the mirror box illusion has proven to be successful in alleviating pain, but also in improving motor function in

CRPS patients (e.g. Bultitude & Rafal, 2010; McCabe, Haigh, Ring, et al., 2003; Tichelaar, Geertzen, Keizer, & van Wilgen, 2007; also see Al Sayegh et al., 2013 for an overview).

Another rehabilitation technique, called prismatic adaptation, is also based on the idea that the symptomatology of CRPS is associated with cognitive dysfunctions affecting body representation (Legrain et al., 2012). Sumitani et al. (2007) found that visual subjective body midline judgments of CRPS patients were deviated towards the painful side. Based on this observation and similar observations in hemispatial neglect patients (Rossetti et al., 1998), the prismatic adaptation technique was developed. During prismatic adaptation, patients perform a visuo-motor pointing task while wearing prismatic goggles that create a lateral shift in the visual field towards the unaffected side. This intervention induces a mismatch between the seen and felt position of the pointing hand and creates after-effects that restore the accurate body representation. This technique, when applied during a period of two weeks, has shown to alleviate pain and to reduce autonomic dysfunction in CRPS patients (Sumitani, Rossetti, et al., 2007; see also Christophe et al., 2016), and underlines the intrinsic relation between pain and spatial (body) perception.

In conclusion, research targeting the relation between spatial (body) perception on the one hand and touch or pain perception on the other hand can be highly relevant in a clinical context. First, approaching patients during clinical examinations might result in biased evaluations of the capacities of the somatosensory system, although further research is necessary to determine the size of such effects and the role of other contextual factors (e.g. pain anticipation, anxiety). Second, based on the close connection between body representation and pain, interesting new rehabilitation techniques such as mirror therapy and prismatic adaptation have been developed that have successfully alleviated pain and disability in chronic pain patients.

LIMITATIONS AND CHALLENGES FOR FUTURE RESEARCH

The studies conducted in this PhD provided new insights into crossmodal interactions between vision and touch in healthy individuals and into the perception of touch in chronic pain patients. However, several issues remain unanswered and require additional research. In what follows, limitations of the present studies discussed and recommendations are made for future studies.

The In Vivo Approaching Object (IVAO) paradigm was newly-developed to investigate the effect of vision upon touch in a dynamic and ecologically valid context. Of course, there were some limitations to this paradigm, but also some interesting new approaches for future research.

First, the visual stimuli used in the IVAO paradigm – i.e. approaching the participant with a neutral object – were not perfectly standardized as the approaching movement was performed by the experimenter and not by a mechanical device (e.g. a robotic arm). Although the experimenter was trained to perform this movement in a standardized manner, small deviations in speed and fluency of the approaching movement could not be prevented. Yet, as the experimenter was never aware of which type of trial was currently running, systematic differences in the approaching movement are very unlikely. On the other hand, we feel that this loss in standardization was only a small cost, compared to the benefit of employing a paradigm that is more ecologically valid than most paradigms used to investigate crossmodal interactions in humans.

Second, although we presume, based on our findings with the IVAO paradigm, that approaching a patient during clinical examinations could result in an overestimation of the capacities of the somatosensory system, we have no information on how large this bias would be, that is, if it could lead to actual misdiagnosis. We propose that future IVAO studies could include other outcome variables that are able to reflect the size of changes in tactile sensitivity, for example by asking participants to rate the intensity of tactile stimuli. Also, it could be interesting to apply signal detection theory analyses that distinguish between 'true' perceptual sensitivity of near-threshold stimuli and criterion measures, by examining hits (outcome measure of IVAO studies in this PhD), misses, false alarms and correct rejections (Macmillan & Creelman, 2005). Moreover, these effects should also be assessed in chronic pain patients, as different mechanisms may underlie spatial (body) perception in chronic pain.

Third, it remains unclear whether the approaching movement in the IVAO paradigm was processed as an exogenous or endogenous stimulus. The study in Chapter 4 suggests that, at least in part, top-down or endogenous attentional processes were active, as demonstrated by the differential outcomes for approaching participants with a pain versus safety signaling pen. However, given the unexpected findings of pain anticipation on visuo-tactile interactions in that study (and in Chapter 5), we argue that additional studies are needed that aim to investigate the exogenous or endogenous processing of watching being approached. One approach could be to assess the effect of visual stimuli with different signal values, but without giving explicit instructions about that signal value (e.g. blue = pain, yellow = safety) that might already affect attentional processes (Filbrich, Torta, Vanderclausen, Azañón, & Legrain, 2016). In contrast, one could make use of the signal value of a stimulus that is already present by default or by previous learning experiences. For example, participants could be approached with either a cotton swab (no pain anticipation) or a syringe (pain anticipation; e.g. see Vandenbroucke, Crombez, Loeys, & Goubert, 2014). If tactile sensitivity upon being approached with a syringe would increase more than when being approached with a cotton swab, this would be direct proof of endogenous components underlying the effect of vision upon touch. More approaches to distinguish between exogenous and endogenous components were already discussed in the respective section of this general discussion and include manipulating the extent to which the direction of the approaching movement predicts the location of tactile stimuli on the hands (i.e. cue validity; see Wright & Ward, 2008). When cue validity is low, the facilitative effect of endogenous cues will fade, as they are no longer regarded as useful and therefore no longer voluntarily attended, whereas the effect of exogenous cues will be unaffected. Related to this, we have no information on interpersonal effects of the experimenter facing and approaching the participant. It would be interesting to know whether differences in task performance or other outcomes would occur, based on gender or status (e.g. doctor in white cloak) of the experimenter.

Fourth, although we were able to establish visuo-tactile interactions by using dynamic visual stimuli, the IVAO paradigm did not allow us to measure these interactions along a spatial continuum (from near to far space). Using a mechanical arm to approach participants would make it possible to explore the boundaries of the peripersonal space or to measure its plasticity. For example, it could be assessed whether the extent of the peripersonal space changes when anticipating pain, or when one limb is affected by CRPS. However, using a mechanical arm – instead of a real person – to approach participants would inevitably diminish the ecological validity of the IVAO paradigm.

There were also some limitations related to the use of the temporal order judgment (TOJ) paradigm, especially in a chronic pain population. First, we noticed that the ability of chronic pain patients to perform the TOJ task was not always optimal, especially when arms were crossed, forcing us to exclude a certain amount of data. Related to this, we observed that chronic pain patients' JND (i.e. just noticeable difference, reflecting temporal sensitivity) values were very high, in some patients even higher than the largest SOA (200ms). This means that, although those patients achieved a minimal task performance of 75% (i.e. criterion for inclusion), they were probably not able to perform the TOJ task adequately, because some of them needed, according to their JND value, a time interval of almost a second to achieve minimal task performance, whereas the largest presented SOA was only 200ms. This suggests that the TOJ paradigm might be less suitable for investigating somatosensory perception in chronic pain populations. As of yet, there are no clear guidelines or criteria for excluding data based on the JND values. We propose that in future research, data from participants with a JND larger than the largest SOA are excluded from analysis.

Second, the main outcome of the TOJ task, the point of subjective simultaneity (PSS) is very sensitive to the number of observations that are available for each condition. A few errors from the participant in responding or from the experimenter in inserting responses can already cause a large shift in the PSS when the number of observations is low. In our TOJ studies, we used a within-subject design, therefore the number of observations was limited (4, 8, or 12, depending on the experiment and analysis). Yet, increasing the number of observations was not regarded an option, as the total number of trials is limited by the attention span of the participants, especially in a chronic pain population.

Third, when we interpreted the outcomes of the TOJ studies, we assumed that these outcomes reflected truly perceptual effects, caused by attentional modulations (e.g. anticipation of pain on one hand). However, we cannot completely exclude the possibility that our results were, at least in part, due to decisional or response biases. Filbrich et al. (2015) argued that when participants are uncertain about which hand was stimulated first (i.e. at smaller SOAs), they might respond in correspondence to the side of space that was instructed to attend. Although we never specifically instructed participants to attend one side of space, it could be that they still responded according to the side that was regarded as more task-relevant (e.g. the threatened side). However, this seems rather unlikely as participants' judgments in our study were biased *away from* the threatened side. Still, several measures can be taken to prevent decisional and response biases from becoming intertwined with perceptual biases. For example, participants could be asked to respond, alternating between blocks, which hand was stimulated *first* and which hand *second*, cancelling out response biases (Spence, Shore, & Klein, 2001). These biases can also be prevented by performing simultaneity judgments, rather than temporal order judgments (Zampini, Guest, Shore, & Spence, 2005). Ideally, response mapping is always orthogonal to the mapping of the visual cues (e.g. cues are presented left or right and targets are presented up or down). This was not the case in our studies, as participants always made left/right-judgments of tactile targets. However, in the pain anticipation study (Chapter 5), foot pedals were used on which participants lifted their toe or heel (up/down) to respond which side was perceived as stimulated first (left/right). It should be noted that the use of up/down foot movements for responding which side was perceived first (left/right) proved to be difficult for participants, which made us decide not to use them in the TOJ study with chronic pain patients.

There were also some general methodological limitations, related to the studies we conducted in this PhD. For example, in the studies in which we manipulated pain anticipation, one would easily presume that the perceptual biases that we observed were specific to the anticipation of pain. However, it was suggested that the function of signaling bodily threats is not restricted to nociceptive stimuli, but can be executed by stimuli from any modality, as long as they are salient enough (Legrain et al., 2011). Therefore, it could be that our results were not specific to the anticipation of pain, but were rather the result of anticipating a relevant or aversive event. Therefore, future studies could include a control condition in which a non-painful, but equally salient, somatosensory stimulus is anticipated. However, it could be that the effect of anticipating pain would still be larger (or different) than the effect of anticipating a non-painful arousing event, due to top-down variables, such as anxiety or worrying about pain.

Finally, there were some limitations, related to the study populations that were used. First, healthy undergraduate students participated in most of our studies. Although this population is easily recruited and generally performs well on attention-demanding cognitive tasks, it is also very homogeneous and quite specific. Therefore, this study population might not be representative for the general population. Furthermore, when targeting chronic pain patients in our clinical study, we experienced recruitment difficulties, especially for CRPS patients. Despite the fact that we set up a multicenter to recruit CRPS patients, low availability of these patients in the clinic and diminishing prevalence of the condition, due to improving care, impeded us to recruit a larger sample of CRPS patients. Therefore, we propose that future studies employ single-case designs and analyses to be able to study the symptomatology and treatment of CRPS in smaller samples. Moreover, we are convinced that such an approach would be more suitable to grasp the complex constellation of symptoms and deficits in patients suffering from CRPS.

CONCLUSION

During this PhD, we investigated processes of spatial perception, especially crossmodal interactions between vision and touch. More specifically, we investigated whether the perception of touch was affected by the presence of visual stimuli approaching the body, and whether such visuo-tactile interactions are facilitated by the anticipation of pain. Moreover, we investigated the perception of touch in patients with complex regional pain syndrome (CRPS) and compared this to the perception of touch in non-CRPS chronic pain patients. First, we found that watching being approached increases tactile sensitivity on the approached body-part, but only when the approaching movement is close to the body, in the peripersonal space. This does not only confirm previous studies on visuo-tactile interactions, but might also be of relevance in a clinical context, in which patients are often approached and touched by doctors. However, additional research is needed to determine the size of this effect on tactile perception, but also to investigate the effect of being approached on the perception of pain. Furthermore, we found that, in the case of visuo-tactile interactions in peripersonal space, the perceived proximity between visual stimuli and the body is both dependent on proprioception (i.e. *feeling* your body being located close to a visual event), and on vision (i.e. *seeing* your body being located close to a visual event). Second, we hypothesized that crossmodal interactions between vision and touch would be facilitated by the anticipation of pain, but found the opposite effect. We propose that the effect of threatening information is not hard-wired, but may depend on a number of contextual factors, such as attentional resources or fear or pain. However, this still needs to be confirmed by future studies. Third, we measured the perception of touch in patients with CRPS and in patients with chronic unilateral shoulder and unilateral wrist pain, and investigated whether biases in tactile perception are dependent on a somatotopic or spatiotopic frame of reference. However, we could not find evidence for systematic biases in the perception of touch in CRPS patients, nor in the non-CRPS chronic pain patients. As individual variability was quite high, we suspect that other variables, such as pain intensity and pain duration, may have an effect on the perception of touch in chronic pain patients.

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NEDERLANDSTALIGE SAMENVATTING

INLEIDING

Vroeg of laat ervaart iedereen pijn in zijn of haar leven. Hoewel een pijnervaring erg divers kan zijn (bv. plots of gradueel, mild or ondraaglijk), is iedereen het erover eens dat pijn een onaangename ervaring is waar we zo snel mogelijk van verlost willen zijn. Toch kan pijn ons in bepaalde gevallen ook behoeden voor lichamelijke schade, doordat het ons motiveert om bedreigende situaties te ontvluchten. Onderzoek rond pijn is jarenlang uitgegaan van het idee dat er een directe relatie bestaat tussen pijn en weefselschade (biomedisch perspectief). Echter, gezien de observatie dat pijn kan blijven voortbestaan of zelfs ontstaan zonder weefselschade, werd het duidelijk dat andere factoren de perceptie van pijn kunnen mee beïnvloeden. Binnen het biopsychosociaal perspectief worden niet enkel biologische factoren, maar ook psychologische en sociale factoren mee in acht genomen in het verklaren van (chronische) pijn (Engel, 1977). Zo werd er binnen de cognitieve psychologie veel aandacht besteed aan de relatie tussen pijn en aandacht. Men observeerde dat pijnprikkels het uitoefenen van secundaire bezigheden (bv. cognitieve taak) kunnen onderbreken, maar evenwel dat het uitvoeren van een bezigheid die veel aandacht vergt ook de perceptie van pijn kan temperen. Daarom kende men twee schijnbaar tegengestelde functies toe aan aandacht voor pijn, namelijk enerzijds (1) het onderbreken van iemands bezigheden en het aanmanen tot het stellen van een adequate reactie (bv. situatie ontvluchten) om verdere schade te voorkomen, (= bottom-up aandacht); en anderzijds (2) het vasthouden van de aandacht zodat andere doelen kunnen behaald worden die belangrijk zijn voor het individu (= top-down aandacht) (Eccleston & Crombez, 1999; Van Damme, Legrain, Vogt, & Crombez, 2010).

De saliëntie-detectie theorie (Legrain, Iannetti, Plaghki, & Mouraux, 2011) beschrijft hoe nociceptieve prikkels automatisch gedetecteerd en geprioriteerd worden, op basis van hun saliëntie, dat is de mate waarin ze contrasteren met andere prikkels (bv. nieuw of intens karakter). Echter, er werd aangetoond dat hersenactiviteit in hersengebieden die tot dan aanzien werden als specifiek voor de verwerking van nociceptieve prikkels (= pijn matrix), evenwel kan uitgelokt worden door niet-nociceptieve prikkels, zoals tactiele, visuele en auditieve prikkels, zolang deze saliënt of relevant genoeg zijn om de aandacht te grijpen (zie Legrain et al., 2011 voor een overzicht). Het unieke karakter van pijn werd daarom meer en meer in vraag gesteld. Op basis van deze bevindingen werd een functioneel perspectief aangenomen ten opzichte van pijn, dat drie belangrijke functies omvat: (1) selectieve aandacht: de detectie en het richten van de aandacht naar de meest saliënte of relevante stimuli zodat hun verwerking geprioriteerd wordt; (2) spatiale perceptie: het lokaliseren van stimuli op het lichaam en in de externe ruimte rondom het lichaam; (3) actie selectie: het selecteren en voorbereiden van de meest geschikte (defensieve) reactie. Zoals gezegd zijn deze functies niet specifiek voor pijn, waardoor de focus niet langer ligt op de perceptie die uitgelokt wordt door nociceptieve prikkels, maar op het kunnen detecteren van relevante of bedreigende gebeurtenissen in de omgeving van het lichaam (Legrain & Torta, 2015). In het huidige doctoraat lag vooral de focus op één van deze functies, namelijk spatiale perceptie.

Wanneer relevante of bedreigende prikkels zich nabij het lichaam bevinden (bv. een aanvallende wesp), is het van belang dat deze opgemerkt word en gelokaliseerd worden, zodat een gepaste (defensieve) reactie kan gesteld worden (bv. de wesp wegslaan of wegvluchten voor de wesp). Hoewel zo'n reactie vrij eenvoudig en automatisch mag lijken, gaan er complexe lokalisatieprocessen aan vooraf. Het lokaliseren van prikkels gebeurt met behulp van interne referentiekaders die de locatie van prikkels coderen volgens bepaalde coördinaten (Colby & Goldberg, 1999; Fogassi et al., 1996). In het kader van dit doctoraat waren we vooral geïnteresseerd in het verschil tussen een somatotopisch en een spatiotopisch referentiekader voor het lokaliseren van prikkels op het lichaam (persoonlijke ruimte) en in het verschil tussen een peripersoonlijk en een extrapersoonlijk referentiekader voor het lokaliseren van prikkels buiten het lichaam (externe ruimte).

Het lokaliseren van prikkels op het lichaam, in de persoonlijke ruimte, is deels afhankelijk van de directe overeenkomst tussen de spatiale organisatie van receptoren op de huid en hun projectie naar specifieke subgroepen van neuronen in de primaire somatosensorische cortex (Narici et al., 1991; Penfield & Boldrey, 1937; Penfield & Rasmussen, 1950). Zo een *somatotopisch referentiekader* laat vooral toe om prikkels op het lichaam te lokaliseren, op basis van de gewoonlijke positie van de ledematen. Echter, wanneer dit niet het geval is, bijvoorbeeld wanneer de armen gekruist zijn en een wesp op de linkerhand zich bijgevolg rechts van het lichaam bevindt, kan een incorrecte lokalisatie van het object – links, in plaats van rechts – ontstaan. Daarom wordt ook een *spatiotopisch referentiekader* gebruikt, dat wel rekening houdt met de positie van de ledematen ten opzichte van elkaar, van het lichaam en van de externe ruimte (Vallar, 1997), waardoor gerichte en gepaste reacties kunnen gevormd worden.

Het lokaliseren van prikkels in de externe ruimte gebeurt volgens een peripersoonlijk of een extrapersoonlijk referentiekader, afhankelijk van de afstand van de prikkels ten opzichte van het lichaam (Halligan & Marshall, 1991). Het *peripersoonlijk referentiekader* is erg relevant voor het beschermen van het lichaam tegen externe bedreigingen, omdat het zowel prikkels op het lichaam (=somatosensorische prikkels) codeert, als prikkels in de externe ruimte, wanneer die zich dichtbij het lichaam bevinden (in de peripersoonlijke ruimte). Zodoende laat dit referentiekader een gerichte manipulatie van externe objecten nabij het lichaam toe (Rizzolatti, Fadiga, Fogassi, & Gallese, 1997). Het *extrapersoonlijk referentiekader* daarentegen maakt via oogbewegingen de exploratie mogelijk van prikkels buiten grijpafstand van het lichaam, en faciliteert hierbij reikbewegingen.

Wanneer relevante of bedreigende gebeurtenissen of objecten gelokaliseerd worden, is het zo dat deze vaak uit prikkels bestaan van verschillende sensorische modaliteiten (bv. men voelt niet enkel de wesp op het lichaam maar ziet en hoort ze ook). Deze multimodale informatie wordt geïntegreerd, zodat een meer stabiele en coherente representatie wordt verkregen van de externe ruimte waarin deze prikkels zich bevinden. Zulke *crossmodale interacties* komen voor tussen vrijwel alle sensorische modaliteiten, maar zijn vooral relevant tussen somatosensorische prikkels, die schade kunnen toebrengen aan het lichaam, en visuele prikkels, die een bedreiging of relevant object kunnen signaleren. Het is dan ook niet verwonderlijk dat crossmodale interacties tussen visuele en tactiele (of nociceptieve) prikkels vooral plaatsvinden nabij het lichaam, in de peripersoonlijke ruimte (bv. De Paepe, Crombez, Spence, & Legrain, 2014; Làdavas, Zeloni, & Farnè, 1998; Spence, Nicholls, Gillespie, & Driver, 1998). Hoewel visuo-tactiele interacties reeds duidelijk aangetoond werden bij mensen, gebeurde dit vooral door middel van statische visuele prikkels (bv. flitsende LED-lampjes). Echter, in het dagdagelijkse leven zijn mensen, en prikkels rondom hun lichaam, meestal in beweging. Vooral wanneer men poogt het lichaam te beschermen tegen externe bedreigingen, zijn prikkels die het lichaam benaderen van potentieel belang, omdat deze een mogelijke impact met het lichaam aangeven. Er is daarom nood aan ecologisch valide studies die het effect onderzoeken van dynamische prikkels, meer bepaald van prikkels die het lichaam benaderen, op de perceptie van prikkels op het lichaam.

Voorgaand onderzoek toonde aan dat de anticipatie van pijn de perceptie van prikkels op het bedreigde lichaamsdeel kan verhogen (Koster, Crombez, Van Damme, Verschuere, & De Houwer, 2004; Vanden Bulcke, Van Damme, Durnez, & Crombez, 2013). Toch werd dit nog niet aangetoond overheen verschillende modaliteiten (bv. visuo-tactiel). Daarom stelt zich de vraag of visuo-tactiele interacties nabij het lichaam zouden beïnvloed worden wanneer men pijn verwacht. Dit zou in overeenstemming zijn met het feit dat de peripersoonlijke ruimte ook wordt omschreven als een defensieve veiligheidsmarge rondom het lichaam. Daarnaast kan ook verwacht worden dat niet enkel de anticipatie van pijn, maar ook (chronische) pijn zelf een invloed heeft op spatiale perceptie. Bijvoorbeeld, bij patiënten met Complex Regionaal Pijnsyndroom (CRPS), een systemische aandoening van één van de bovenste of onderste ledematen (Marinus et al., 2011), werd een vertekening in de perceptie van tactiele prikkels gevonden, waarbij prikkels op de gezonde hand geprioriteerd werden, ten nadele van prikkels op de pijnlijke hand (Moseley, Gallace, & Spence, 2009). Echter, wanneer deze patiënten hun armen gekruist hadden, werden prikkels op de pijnlijke hand geprioriteerd. Dit toont aan dat de verstoring van de perceptie van tactiele prikkels bij deze patiënten niet gebonden is aan de geaffecteerde hand (of afhangt van een somatotopisch referentiekader), maar gebonden is aan dit deel van de ruimte waarin de geaffecteerde hand zich normaal bevindt (en dus afhangt van een spatiotopisch referentiekader). Niettemin bestaat er nog geen duidelijkheid over de richting en oorzaken van zulke perceptuele vertekeningen bij CRPS patiënten, gezien andere studies tegengestelde effecten observeerden (Reinersmann et al., 2012; Sumitani et al., 2007; Uematsu et al., 2009). Ook is er tot op heden weinig geweten over de generaliseerbaarheid van de perceptuele symptomen van CRPS patiënten naar andere chronische pijn populaties (zie Kolb, Lang, Seifert, & Maihöfner, 2012).

Kortom, dit geeft het belang aan van het onderzoeken van spatiale perceptie, om de normale verwerking en perceptie van tactiele informatie (bv. visuo-tactiele interacties nabij het lichaam) te bestuderen, maar ook om de verstoorde perceptie van tactiele informatie bij chronische pijn patiënten beter te begrijpen.

DOELSTELLINGEN

Het doel van deze doctoraatsthesis was het onderzoeken van spatiale perceptie, in hoofdzaak crossmodale interacties tussen visuele en tactiele prikkels, onder verschillende omstandigheden, namelijk: (1) wanneer visuele prikkels het lichaam benaderen (dynamische context); (2) wanneer pijn op het lichaam geanticipeerd wordt (bedreigende context); en (3) bij patiënten met chronische pijn, waaronder CRPS.

Ten eerste onderzochten we het effect van visuele prikkels die het lichaam benaderen op de perceptie van tactiele prikkels. Hiervoor ontwikkelden we het In Vivo Approaching Object (IVAO) paradigma waarin proefpersonen benaderd werden met een neutraal object, gelijkend op een pen en gehanteerd door de proefleider. We verwachtten dat de gevoeligheid voor tactiele prikkels op het lichaam zou verhoogd zijn wanneer proefpersonen dit lichaamsdeel zagen benaderd worden door de proefleider (= visuo-tactiele interactie). Daarenboven verwachtten we dat deze visuo-tactiele interacties vooral zouden optreden wanneer de benaderende beweging dichtbij het lichaam plaatsvond (in de peripersoonlijke ruimte), in tegenstelling tot verder van het lichaam (in de extrapersoonlijke ruimte).

Ten tweede werd onderzocht of visuo-tactiele interacties gefaciliteerd worden tijdens de anticipatie van pijn op het lichaam. Hiervoor werd de IVAO taak gebruikt, maar ook de temporal order judgment (TOJ) taak, waarin vertekeningen in de perceptie van tactiele prikkels kunnen worden gemeten, afhankelijk van manipulaties van de spatiale aandacht (Spence & Parise, 2010). We verwachtten dat het effect van visuele prikkels op tactiele perceptie sterker zou zijn op dat deel van het lichaam waarop pijn werd geanticipeerd.

Ten derde werd de perceptie van tactiele prikkels onderzocht bij patiënten met CRPS, gebaseerd op de studie van Moseley en collega's (2009). Bovendien werd dit systematisch vergeleken met twee controlegroepen, bestaande uit chronisch unilaterale polspijn patiënten en chronisch unilaterale schouderpijn patiënten. In de CRPS groep werd verwacht dat de perceptie van tactiele prikkels zou vertekend zijn, ten nadele van de pijnlijke hand, wanneer de armen in zich in een normale positie bevonden. Wanneer armen gekruist waren, werd een tegengesteld effect verwacht, namelijk een vertekening ten nadele van de niet-pijnlijke hand (= bewijs spatiotopisch referentiekader). In de groep polspijn en schouderpijn patiënten werd een vertekening verwacht ten voordele van de pijnlijke hand, die gebonden was aan de pijnlijke hand.

BEVINDINGEN

DEEL 1

In deel 1 werden bij gezonde proefpersonen crossmodale interacties tussen visuele en tactiele informatie in de peripersoonlijke ruimte onderzocht in een dynamische en ecologisch valide context.

In **hoofdstuk 1** werd het nieuw ontwikkelde In Vivo Approaching Object (IVAO) paradigma uitgetest. De proefleider benaderde de linker- of rechterhand van proefpersonen met een neutraal object, gelijkend op een pen, van dichtbij (peripersoonlijke ruimte) of van verderaf (extrapersoonlijke ruimte). Dit werd in de helft van de gevallen onmiddellijk gevolgd door een zeer lichte (niveau gevoelsdrempel) tactiele prikkel op de benaderde hand, de tegenovergestelde hand, of op beide handen tegelijkertijd. In de overige gevallen werd geen tactiele prikkel toegediend. De accuraatheid waarmee proefpersonen de tactiele prikkels detecteerden en lokaliseerden werd berekend en vergeleken tussen de benaderde en de niet-benaderde hand, zowel dichtbij als veraf. Er werd verwacht dat de gevoeligheid voor tactiele prikkels hoger zou zijn voor de benaderde hand dan voor de tegengestelde hand, vooral in de peripersoonlijke ruimte. Echter, deze hypothese kon niet bevestigd worden, wellicht omwille van toenmalige methodologische beperkingen van het IVAO paradigma.

In **hoofdstuk 2** werden een aantal methodologische wijzigingen aangebracht om het IVAO paradigma te optimaliseren. Dezelfde onderzoeksvragen (visuo-tactiele interacties in de peripersoonlijke ruimte) werden onderzocht als in hoofdstuk 1. In Experiment 1 werden proefpersonen opnieuw benaderd naar de linker- of rechterhand, maar enkel van dichtbij. Dit werd gevolgd door een lichte tactiele prikkel op dezelfde hand, op de tegenovergestelde hand, op beide handen tegelijkertijd, of door de afwezigheid van een tactiele prikkel. In Experiment 2 werd een conditie toegevoegd waarin proefpersonen ook benaderd werden van verderaf. Tactiele gevoeligheid werd opnieuw berekend en vergeleken tussen de benaderde en de niet-benaderde hand, zowel dichtbij als veraf. Zoals verwacht was de tactiele gevoeligheid hoger voor het benaderde lichaamsdeel, vooral wanneer de benaderende beweging dichtbij het lichaam plaatsvond. Deze resultaten bevestigden het bestaan van crossmodale interacties tussen visuele en tactiele informatie in de peripersoonlijke ruimte, in een dynamische en ecologisch valide context.

In **hoofdstuk 3** werd het IVAO paradigma aangepast om de rol van visuele informatie, los van proprioceptie (= kennis van de stand van de ledematen), te onderzoeken in het ontstaan van visuo-tactiele interacties. We onderzochten of het inschatten van de nabijheid van een visuele prikkel ten opzichte van het lichaam afhankelijk is van visuele informatie over deze afstand of door proprioceptieve informatie over deze afstand. In een eerste conditie werden de handen van de proefpersonen afgedekt zodat kon onderzocht worden of een effect ontstond van het benaderen van de (onzichtbare) handen op de tactiele gevoeligheid. In een tweede conditie werden rubberen handen geplaatst voor de proefpersonen, overeenkomstig met de stand van de echte handen, zodat de rubberen handen de echte handen leken (= rubberen hand illusie). In deze conditie werd onderzocht of het benaderen van fake handen ook de tactiele gevoeligheid kon verhogen op de echte handen, afhankelijk van de mate van belichaming van de rubberen handen (= het gevoel dat de rubberen handen tot het eigen lichaam behoren). We vonden dat de tactiele gevoeligheid hoger was voor de benaderde hand dan voor de niet-benaderde hand, vooral wanneer de rubberen handen benaderd werden. Het effect van belichaming van de rubberen handen was onduidelijk. Deze resultaten toonden aan dat hoewel visuo-tactiele interacties kunnen ontstaan op basis van uitsluitend proprioceptieve informatie, deze sterker zijn wanneer ook visuele informatie beschikbaar is over de nabijheid van naderende objecten tot het lichaam.

DEEL 2

In het tweede deel onderzochten we bij gezonde proefpersonen of visuo-tactiele interacties gefaciliteerd worden tijdens de anticipatie van pijn.

In **hoofdstuk 4** werd het IVAO paradigma aangepast om visuo-tactiele interacties tijdens de anticipatie van pijn te onderzoeken. Proefpersonen werden benaderd met een blauwe of gele pen, gevolgd door een lichte tactiele prikkel op dezelfde hand, op de tegenovergestelde hand, op beide handen tegelijkertijd, of door de afwezigheid van een tactiele prikkel. De instructie werd gegeven dat één van beide pennen af en toe kon gevolgd worden door een pijnlijke prikkel op de benaderde hand (pijnsignaal), terwijl de andere pen nooit kon gevolgd worden door een pijnlijke prikkel (veiligheidssignaal). Op basis van voorgaande studies verwachtten we dat de tactiele gevoeligheid zou verhoogd zijn voor het benaderde lichaamsdeel (= visuo-tactiele interactie), maar vooral wanneer op dat lichaamsdeel ook pijn verwacht werd. Echter, we vonden evidentie voor visuo-tactiele interacties, maar niet voor het faciliterende effect van pijn anticipatie. In tegendeel, we vonden dat de anticipatie van pijn het effect van de benaderende beweging op de tactiele gevoeligheid verstoorde. Verder onderzoek is nodig om deze bevindingen te verzoenen met de huidige literatuur rond het effect van pijnanticipatie en lichamelijke dreiging op somatosensorische perceptie.

In **hoofdstuk 5** onderzochten we opnieuw het effect van pijnanticipatie op visuo-tactiele interacties, ditmaal gebruik makend van het Temporal Order Judgment (TOJ) paradigma. Proefpersonen beoordeelden de temporele volgorde (“welke hand eerst gevoeld?”) van paren van tactiele prikkels, waarvan één prikkel toegediend werd op iedere hand. Dit werd voorafgegaan door een visuele prikkel (= cue) aan dezelfde kant, aan de tegenovergestelde kant of aan beide kanten tegelijkertijd, ofwel dichtbij de handen (peripersoonlijke ruimte) of ver van de handen (extrapersoonlijke ruimte). Daarenboven werden proefpersonen geïnstrueerd dat één van beide handen af en toe een pijnlijke prikkel kon toegediend krijgen. We vonden dat de verwerking van tactiele prikkels geprioriteerd werd aan de gecuede kant (= visuo-tactiele interacties), maar enkel wanneer de cues dichtbij getoond werden (in de peripersoonlijke ruimte). Echter, dit effect werd gevonden voor de niet bedreigde hand, maar niet voor de hand waarop pijn verwacht werd. Dit toont opnieuw aan dat aandacht voor lichamelijke dreiging niet per se een vastliggend fenomeen is maar afhankelijk kan zijn van allerlei contextuele factoren, zoals de beschikbaarheid van aandachtbronnen of vrees voor pijn.

DEEL 3

In deel 3 werd onderzocht hoe de perceptie van tactiele prikkels beïnvloed wordt door chronische pijn, meer bepaald door Complex Regionaal Pijnsyndroom.

In **hoofdstuk 6** repliceerden we de TOJ studie van Moseley et al. (2009) rond de perceptie van tactiele prikkels bij CRPS patiënten (zie eerder), en vergeleken we deze resultaten systematisch met een groep chronisch unilaterale polspijn patiënten en een groep chronisch unilaterale schouderpijn patiënten. Proefpersonen beoordeelden de temporele volgorde van paren van tactiele prikkels, één toegediend op elke hand, met de armen in een normale positie of met de armen gekruist. We verwachtten bij CRPS patiënten een vertekening van de perceptie van tactiele prikkels, weg van de pijnlijke hand (= prioritering van tactiele prikkels op de niet-pijnlijke hand) wanneer de armen zich in een normale positie bevonden, en een vertekening in de richting van de pijnlijke hand (= prioritering van tactiele prikkels op de pijnlijke hand) wanneer de armen gekruist waren. Bij polspijn en schouderpijn patiënten verwachtten we een vertekening in de richting van de pijnlijke hand, ongeacht de armpositie. We vonden geen systematische vertekening in de perceptie van tactiele prikkels op de handen in de CRPS groep, noch in de controlegroepen. De individuele variabiliteit in de resultaten was erg hoog, wat ons doet vermoeden dat andere variabelen een rol speelden, zoals pijnintensiteit of duur van de symptomen. Bijkomend onderzoek is nodig om meer duidelijkheid te scheppen in de perceptie van tactiele informatie bij chronische pijn. Toekomstig onderzoek zou kunnen gebruik maken van een single-case benadering, om de lage prevalentie en beschikbaarheid van CRPS patiënten op te vangen.

CONCLUSIE

In deze doctoraatsthesis hebben we bij gezonde proefpersonen visuo-tactiele interacties in de peripersoonlijke ruimte onderzocht, in een dynamische context en tijdens de anticipatie van pijn, en hebben we bij chronische pijn patiënten, waaronder CRPS patiënten, vertekeningen in de perceptie van tactiele informatie onderzocht. Ten eerste hebben we evidentie gevonden voor visuo-tactiele interacties nabij het lichaam, in de peripersoonlijke ruimte, via een ecologisch valide paradigma dat gebruik maakte van dynamische (benaderende) visuele prikkels. Hoewel meer onderzoek nodig is om de grootte van deze effecten na te gaan, zijn klinische implicaties niet ondenkbaar. Zo worden patiënten tijdens klinische onderzoeken vaak benaderd en aangeraakt door de arts, waarbij de daaropvolgende lichamelijke sensaties (bv. hypoesthesie) kunnen vertekend zijn door het zien van de benaderende beweging van de arts. Ten tweede hebben we aangetoond dat visuo-tactiele interacties niet gefaciliteerd, maar verstoord worden wanneer pijn wordt verwacht op het lichaam. Dit toont aan dat aandacht voor bedreigende informatie niet per se een vaststaand fenomeen is, maar kan afhangen van contextuele factoren, zoals bijvoorbeeld de beschikbaarheid van aandachtbronnen of vrees voor pijn. Meer onderzoek is echter nodig om de rol van deze factoren in kaart te brengen. Ten derde onderzochten we de perceptie van tactiele informatie bij chronische pijn patiënten, waaronder patiënten met CRPS. We vonden geen evidentie voor vertekeningen in de perceptie van tactiele informatie in deze patiëntengroepen. Individuele variabiliteit in de resultaten was erg groot, wat ons doet vermoeden dat andere variabelen, zoals pijnintensiteit of de duur van de symptomen, een rol kunnen spelen bij het ontstaan van verstoringen in de perceptie van tactiele informatie bij chronische pijn patiënten.

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Valéry, I'd like to thank you as well, for being a part of my PhD journey. Although I was always nervous to receive your feedback on my papers, you always managed to lift the quality of my work, and to encourage me, each time, to learn more about my research subject. Even though the distance between Ghent and Brussels sometimes felt as an unfortunate barrier, you always managed to contribute to my work when needed. Merci pour tout, Valéry.

Ook bedankt aan de leden van mijn begeleidingscommissie, Prof. Stefaan Van Damme, Prof. Durk Talsma en Prof. Marcel Brass, voor de boeiende discussies en commentaren tijdens onze jaarlijkse samenkomsten.

Collega's, ook jullie wil ik bedanken. Jullie steun en interesse waren hartverwarmend, in het bijzonder gedurende de laatste maanden van het doctoraatsavontuur, wanneer de zenuwen soms (lees: bijna steeds) strak gespannen stonden. Een aantal mensen wil ik hierbij extra in de bloemetjes zetten.

Dimi, je rol als peter heb je met glans vervuld. Niet enkel in het begin van mijn doctoraat hielp je me met plezier op weg met allerlei technische snufjes, maar ook doorheen mijn doctoraat was je telkens oprecht geïnteresseerd in hoe het met me ging. Iedereen mag blij zijn met een collega zoals jij!

Annick, samen verkenden wij de peripersoonlijke ruimte, van veraf tot dichtbij. Ook jou wil ik bedanken, om de eerste stenen te leggen van ons mini 'spatial perception'-teampje, maar ook voor jouw blijvende interesse en advies tijdens onze gezamenlijke vergaderingen.

Sara, Elke en Marieke, wat leuk dat jullie er waren om af en toe eens het doctoraat te vergeten en te klinken op de rest van het leven! Sara, vooral mijn bijzondere appreciatie voor jouw medeleven in tijden van zorgen en paniek (samen mijn to-do lijstjes overlopen en me verzekeren dat het vast zou goed komen) en voor het leveren van de nodige afleiding en hilariteit op de overige momenten (een trouwkleed kiezen is ook zoveel leuker dan een doctoraat schrijven!). Top-collega!

Uiteraard wil ik ook mijn familie bedanken. Mama en papa, oma en opa, het zijn jullie die het in de eerste plaats mogelijk gemaakt hebben voor mij tot hier te geraken. Opa, jij leerde me als eerste lezen (een onmisbare vaardigheid binnen de academische wereld!) en stimuleerde me om het beste uit mezelf te halen. Papa, jij wakkerde mijn interesse aan in wetenschap en psychologie, en timmerde zo mee aan de weg die nu bewandel. Ik werd door jullie aangemoedigd om steeds hoog te mikken en door te zetten en daarvoor ben ik eeuwig dankbaar.

Santina, het afgelopen jaar zaten wij beiden aan onze bureau gekluisterd, in search of diplomas. Gelukkig was er ook voldoende tijd om leuke uitstapjes te maken en onze batterijtjes op te laden voor een nieuwe werk-/studieweek. Heel erg bedankt voor je steun en aanwezigheid!

En ten slotte, is er één persoon die overblijft die er meer dan wie ook voor gezorgd heeft dat ik dit heb kunnen bereiken. Jens, liefje, geen thesis van 325 pagina's zal ooit kunnen weergeven hoezeer ik je dankbaar ben dat je me bijgestaan hebt in deze reis. Jij was er als eerste bij op lastige momenten en vormde een onuitputtelijke bron van geduld en aanmoediging. Ik kan alleen maar hopen hetzelfde voor jou te kunnen betekenen op het einde van jouw academische reis, en in de rest van ons leven. Bedankt, voor alles.

Lien,
september 2016

DATA STORAGE FACT SHEETS

DATA STORAGE FACT SHEET (09/09/16)

% Data Storage Fact Sheet
% Name/identifier study:/
% Author: Lien Van der Biest
% Date: 09/09/16

1. Contact details
==

1a. Main researcher

- name: Lien Van der Biest
- address: Henri Dunantlaan 2 - 9000 Gent - Belgium
- e-mail: Livdrbie.VanderBiest@UGent.be

1b. Responsible Staff Member (ZAP)

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

If a response is not received when using the above contact details, please send an email to data.pp@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:

Van der Biest, L. (2016). The In Vivo Approaching Object paradigm: a pilot study. PhD Dissertation, Chapter 1.

* Which datasets in that publication does this sheet apply to?:all data

3. Information about the files that have been stored
==

3a. Raw data
----

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

* On which platform are the raw data stored?
- [X] researcher PC
- [X] research group file server

- [ ] responsible ZAP PC

* Who has direct access to the raw data (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): ...

3b. Other files
----

* Which other files have been stored?
- [X] file(s) describing the transition from raw data to reported results.
Specify: set-by-step manual on how to calculate outcome variables in this study (TDA)

-IVAO-1_manual raw to processed data

- [X] file(s) containing processed data.
Specify:
-IVAO-1_processed data.xlsx
-IVAO-1_data on accuracy.sav
-IVAO-1_data on questionnaires.xlsx

- [X] file(s) containing analyses.
Specify:
-IVAO-1_analyses on accuracy.spv

- [X] files(s) containing information about informed consent
Specify: a blank copy is saved on the PC of the main researcher

- [ ] 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: see manual raw to processed data

- [X] other files. Specify: file on which participants were excluded from the analyses
-IVAO-1_overview excluded participants.xlsx

* On which platform are these other files stored?
- [X] individual PC
- [X] research group file server
- [ ] 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
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2. Information about the datasets to which this sheet applies
==
* Reference of the publication in which the datasets are reported:

Van der Biest, L. (2016). Watching what's coming near increases tactile sensitivity: an experimental investigation. PhD Dissertation, Chapter 2.

Van der Biest, L., Legrain, V., De Paepe, A., Crombez, G. (2016). Watching what's coming near increases tactile sensitivity: an experimental investigation. Behavioural Brain Research, 297, 307-314.

* Which datasets in that publication does this sheet apply to?:all data

3. Information about the files that have been stored
==

3a. Raw data

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

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- [X] researcher PC
- [X] research group file server
- [ ] responsible ZAP PC

* Who has direct access to the raw data (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): ...

3b. Other files

----

* Which other files have been stored?
- [X] file(s) describing the transition from raw data to reported results.
Specify: step-by-step manual on how to calculate outcome variables in this study (TDA values)

    -IVAO-2-3_manual raw to processed data.docx

- [X] file(s) containing processed data.
Specify:
    -IVAO-2_processed data.xlsx
    -IVAO-2_data on accuracy.sav
    -IVAO-2_data on questionnaires.xlsx
    -IVAO-2_data on post-block items.sav
    -IVAO-2_data on tactor intensities.sav

    -IVAO-3_processed data.xlsx
    -IVAO-3_data on accuracy.sav
    -IVAO-3_data on questionnaires.xlsx
    -IVAO-3_data on post-block items.sav
    -IVAO-3_data on tactor intensities.sav

- [X] file(s) containing analyses.
Specify:
    -IVAO-2_analyses on accuracy.R
    -IVAO-2_analyses on post-block items.spv
    -IVAO-2_analyses on tactor intensities.spv

-IVAO-3_analyses on accuracy.R
-IVAO-3_analyses on post-block items.spv
-IVAO-3_analyses on tactor intensities.spv
-IVAO-3_analyses on perceptual thresholds by hand dominance.spv

- [X] files(s) containing information about informed consent
Specify: a blank copy is saved on the PC of the main researcher

- [ ] 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: see manual raw to processed data

- [X] other files. Specify: file on which participants were excluded from the analyses
-IVAO-2_overview excluded participants.xlsx
-IVAO-3_overview excluded participants.xlsx

* On which platform are these other files stored?
- [X] individual PC
- [X] research group file server
- [ ] responsible ZAP PC

* Who has direct access to these other files (i.e., without intervention of another person)?
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- [X] responsible ZAP
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2. Information about the datasets to which this sheet applies
==
* Reference of the publication in which the datasets are reported:

Van der Biest, L. (2016). Seeing “your” rubber hands being touched increases tactile sensitivity. PhD Dissertation, Chapter 3.

* Which datasets in that publication does this sheet apply to?:all data

3. Information about the files that have been stored
==

3a. Raw data
----

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

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- [ ] responsible ZAP PC

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- [ ] other (specify): ...

3b. Other files
----

* Which other files have been stored?
- [X] file(s) describing the transition from raw data to reported results.
Specify: set-by-step manual on how to calculate outcome variables in this study (TDA)

-IVAO-RH_manual raw to processed data

- [X] file(s) containing processed data.
Specify:
-IVAO-RH_processed data.xlsx
-IVAO-RH _data on accuracy + RHI items.sav
-IVAO-RH _data on questionnaires.xlsx
-IVAO-RH _data on post-block items.xlsx
-IVAO-RH _data on tactor intensities.xlsx

- [X] file(s) containing analyses.
Specify:
-IVAO-RH _analyses on accuracy + RHI items.R
-IVAO-RH _analyses on RHI items.xlsx
-IVAO-RH _analyses on tactor intensities.xlsx

- [X] files(s) containing information about informed consent
Specify: a blank copy is saved on the PC of the main researcher

- [ ] 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: see manual raw to processed data

- [X] other files. Specify: file on which participants were excluded from the analyses
-IVAO-RH_overview excluded participants.xlsx

* On which platform are these other files stored?
- [X] individual PC
- [X] research group file server
- [ ] responsible ZAP PC

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

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2. Information about the datasets to which this sheet applies
==
* Reference of the publication in which the datasets are reported:

Van der Biest, L. (2016). An approaching object that signals pain disrupts visuo-tactile interactions. PhD Dissertation, Chapter 4.

* Which datasets in that publication does this sheet apply to?:all data

3. Information about the files that have been stored
==

3a. Raw data
----

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

* On which platform are the raw data stored?
- [X] researcher PC
- [X] research group file server

- [ ] responsible ZAP PC

* Who has direct access to the raw data (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): ...

3b. Other files
----

* Which other files have been stored?
- [X] file(s) describing the transition from raw data to reported results.
Specify: set-by-step manual on how to calculate outcome variables in this study (TDA)

    -IVAO-threat_manual raw to processed data

- [X] file(s) containing processed data.
Specify:
    -IVAO-threat_processed data.xlsx
    -IVAO-threat_data on accuracy.sav
    -IVAO-threat_data on post-block items.xlsx
    -IVAO-threat_data on TS and ECS intensities.xlsx

- [X] file(s) containing analyses.
Specify:
    -IVAO-threat_analyses on accuracy.R
    -IVAO-threat_analyses on post-block items.xlsx
    -IVAO-threat_analyses on TS and ECS intensities.xlsx

- [X] files(s) containing information about informed consent
Specify: a blank copy is saved on the PC of the main researcher

- [ ] 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: see manual raw to processed data

- [X] other files. Specify: file on which participants were excluded from the analyses
    -IVAO-threat_overview excluded participants.xlsx

* On which platform are these other files stored?
- [X] individual PC
- [X] research group file server
- [ ] 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): ...

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2. Information about the datasets to which this sheet applies
==
* Reference of the publication in which the datasets are reported:

Van der Biest, L. (2016). Does pain anticipation affect crossmodal interactions between vision and touch? PhD Dissertation, Chapter 5.

* Which datasets in that publication does this sheet apply to?:all data

3. Information about the files that have been stored
==

3a. Raw data
----

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

* On which platform are the raw data stored?
- [X] researcher PC
- [X] research group file server

- [ ] responsible ZAP PC

* Who has direct access to the raw data (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): ...

3b. Other files
----

* Which other files have been stored?
- [X] file(s) describing the transition from raw data to reported results.
Specify: step-by-step manual on how to calculate and interpret outcome variables in this study (PSS and JND values)

-TOJ-1_manual raw to processed data.docx

- [X] file(s) containing processed data.
Specify:
-TOJ-1_processed data on PSS and JND values.xlsx
-TOJ-1_data on PSS and JND values.sav
-TOJ-1_data on questionnaires.sav
-TOJ-1_data on intensities TS and ECS.sav

- [X] file(s) containing analyses.
Specify:
-TOJ-1_analyses on PSS and JND values.spv
-TOJ-1_analyses on questionnaire data.spv
-TOJ-1_analyses on intensities TS and ECS.sav

- [X] files(s) containing information about informed consent
Specify: a blank copy is saved on the PC of the main researcher

- [ ] 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: ...
-See manual raw to processed data.

- [X] other files. Specify: file on which participants were excluded from the analyses
-TOJ-1_overview excluded participants.xlsx

* On which platform are these other files stored?
- [X] individual PC
- [X] research group file server
- [ ] 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

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2. Information about the datasets to which this sheet applies
==
* Reference of the publication in which the datasets are reported:

Van der Biest, L. (2016). An investigation of perceptual biases in Complex Regional Pain Syndrome. PhD dissertation, Chapter 6.

* Which datasets in that publication does this sheet apply to?:all data

3. Information about the files that have been stored
==

3a. Raw data
----

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

* On which platform are the raw data stored?
- [X] researcher PC
- [X] research group file server

- [ ] responsible ZAP PC

* Who has direct access to the raw data (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): ...

3b. Other files
----

* Which other files have been stored?
- [X] file(s) describing the transition from raw data to reported results.
Specify:
 -TOJ-CRPS_manual raw to processed data.docx
 (step-by-step manual on how to calculate and interpret PSS and JND values in this study)

- [X] file(s) containing processed data.
Specify:
 -TOJ-CRPS_processed PSS and JND values_CRPS.xlsx
 -TOJ-CRPS_processed PSS and JND values_wrist.xlsx
 -TOJ-CRPS_processed PSS and JND values_shoulder.xlsx
 -TOJ-CRPS_data on PSS and JND values.sav

 -TOJ-CRPS_data on intensities TS.sav
 -TOJ-CRPS_data on post-block items.sav
 -TOJ-CRPS_data on diagnostic screening.xlsx

- [X] file(s) containing analyses.
Specify:
 -TOJ-CRPS_analyses on PSS and JND values.spv
 -TOJ-CRPS_analyses on intensities TS.spv
 -TOJ-CRPS_analyses on post-block items.spv

- [X] files(s) containing information about informed consent
Specify: a blank copy is saved on the PC of the main researcher

- [X] a file specifying legal and ethical provisions.
Specify:
 -TOJ-CRPS_ethical approval CRPS_Central EC.pdf
 -TOJ-CRPS_ethical approval CRPS_Local EC AZMMSJ.docx
 -TOJ-CRPS_ethical approval UP_Central EC.pdf

- [X] file(s) that describe the content of the stored files and how this content should be interpreted. Specify: Protocol TOJ-CRPS Study

 -TOJ-CRPS_Study Protocol.docx

- [X] other files. Specify: file on which participants were excluded from the analyses
    -TOJ-CRPS_overview excluded participants.xlsx

* On which platform are these other files stored?
- [X] individual PC
- [X] research group file server
- [ ] responsible ZAP PC

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- [X] main researcher
- [X] responsible ZAP
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