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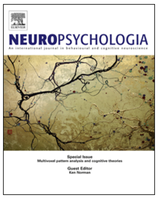

# Mapping nociceptive stimuli in a peripersonal frame of reference: Evidence from a temporal order judgment task

Annick L. De Paepe [a,*], Geert Crombez [a], Charles Spence [b], Valéry Legrain [a,c]

[a] Department of Experimental-Clinical and Health Psychology, Ghent University, Henri Dunantlaan 2, 9000 Ghent, Belgium
[b] Crossmodal Research Laboratory, Department of Experimental Psychology, University of Oxford, UK
[c] Institute of Neuroscience, Université catholique de Louvain, Belgium

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ABSTRACT

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

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## 1. Introduction

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

Furthermore, the representation of external space can be dissociated into peripersonal and extrapersonal frames of reference, coding respectively the position of stimuli arising close to vs. far from the body (Halligan & Marshall, 1991). Interestingly, the peripersonal frame of reference codes both the position of somatosensory stimuli on the body surface and the position of stimuli in external space (e.g., visual stimuli), when they are seen close to the body; it therefore allows an individual to coordinate the map of the body and the map of external close space into an integrated multisensory representation of space (Cardinali, Brozzoli, & Farnè, 2009; Rizzolatti, Scandolara, & Gentilucci, 1981; Spence & Driver, 2004). Whereas the external frame of reference is particularly relevant to guiding the preparation of reaching movements, the representation of peripersonal space is believed to be involved in the direct (i.e., without reaching movement) manipulation of objects in external space (Rizzolatti, Fadiga, Fogassi, & Gallese, 1997). Moreover, it is also believed to be part of a cortical defensive system, designed to trigger defensive motor actions (Graziano & Cooke, 2006).

The existence of a peripersonal frame of reference has been well-documented for the mapping of tactile stimuli (see Spence &

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* Corresponding author. Tel.: +32 9 264 86 11; fax: +32 9 264 64 89.
*E-mail address:* Annick.DePaepe@Ugent.be (A.L. De Paepe).

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Driver, 2004). It is supposed to rely on the existence of multisensory neurons that respond to the stimulation of a specific body-part and to stimuli/events that occur close to that body-part (see Graziano & Gross, 1994). However, as yet, there is no experimental evidence to demonstrate that nociceptive inputs are integrated with visual information into a peripersonal representation of the body and the space that surrounds it (Haggard, Iannetti, & Longo, 2013). Such integration is important because, while touch provides information about object features such as shape and contrast, nociception warns the brain about potential harm of the body, and about the occurrence of threats in external space. Surprisingly, most studies that have investigated the abilities to localize pain rely on the description of the somatotopic organization of the neuronal responses to nociceptive and painful stimuli (Andersson et al., 1997; Baumgartner et al., 2010; Bingel et al., 2004; Henderson, Gandevia, & Macefield, 2007). Only recently have authors started to investigate the ability to localize pain according to non-somatotopic frames of reference~~s~~. For instance, Sambo et al. (2013) and Gallace, Torta, Moseley, and Iannetti (2011) have demonstrated that crossing the hands over the body midline affects judgments concerning the temporal order of nociceptive stimuli delivered to the left and right hand. It has also been shown to reduce the perception of pain. These effects suggest that nociception and pain are sensitive to the conflict, induced by crossing the hands, between a somatotopic representation of the body (defining the anatomical identity of the stimulated limbs) and a spatiotopic representation (defining the position of the stimulated limbs in external space; see Shore, Spry, & Spence, 2002). Similarly, Moseley, Gallace, and Spence (2009) have shown that unilateral chronic pain, such as in complex regional pain syndrome (CRPS), a chronic pain disorder characterized by unilateral sensory, autonomous, vasomotor and motor/trophic dysfunctions, affects the spatiotopic representation of personal space. Other experiments (Sambo, Forster, Williams, & Iannetti, 2012a; Sambo, Liang, Cruccu, & Iannetti, 2012b and Sambo and Iannetti 2013) indicated that the hand blink reflex (HBR), triggered by high-intensity stimulations of the median nerve, was enhanced when the stimulated hand was close to the eyes. However, as no *external* visual stimuli (i.e. outside the personal space) were used in these experiments, it is still a matter of debate as to whether the HBR enhancement by somatic threats is supported by integration of the somatic threat into a peripersonal frame of the face. Using a different experimental paradigm, Van Ryckeghem et al. (2011) and Favril, Mouraux, Sambo, and Legrain (in press) have both shown crossmodal links in spatial attention between nociceptive/painful stimuli and proximal visual stimuli. However, up until now, it has been difficult to disentangle whether these effects are due to the lateralization of the stimuli (left vs. right space) or to their occurrence in the proximity of the body.

In the present study we investigated whether the spatial localization of nociceptive stimuli can be processed according to a peripersonal frame of reference. We tested whether the processing of nociceptive inputs is influenced by the occurrence of external, e.g., visual stimuli, especially when these external stimuli are delivered in the proximity of the stimulated body part. To this end, participants made temporal order judgments (TOJs) concerning which of two nociceptive stimuli, one presented to either hand, had been presented first. Analysis of the resulting data allows for the determination of the stimulus onset asynchrony (SOA) at which two stimuli are perceived to be presented simultaneously. This is known as the Point of Subjective Simultaneity (PSS; Spence, Shore, & Klein, 2001; Zampini et al., 2007).

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

## 2. Methods

### 2.1. Experiment 1

#### 2.1.1. Participants

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

#### 2.1.2. Stimuli and apparatus

The nociceptive stimuli were delivered by means of intra-epidermal electrical stimulation (IES) (DS7 Stimulator, Digitimer Ltd, UK), with stainless steel concentric bipolar electrodes (Nihon Kohden, Japan; Inui, Tsuji, & Kakigi, 2006). The electrodes consisted of a needle cathode (length: 0.1 mm, Ø: 0.2 mm) surrounded by a cylindrical anode (Ø: 1.4 mm). By gently pressing the device against the participant's skin, the needle electrode was inserted into the epidermis of the dorsum of the hand in the sensory territory of the superficial branch of the radial nerve. This method was shown to activate selectively the free nerve endings of the Aδ fibers (Inui et al., 2006; Mouraux, Iannetti, & Plaghki, 2010). In order to guarantee the selective activation of the nociceptors, and in order to avoid co-activation of non-nociceptive Aβ-fiber mechanoreceptors, a strict procedure was used to individually adjust the intensity of the stimulus to two times the detection threshold with an electrical current intensity that was as low as possible (Legrain & Mouraux, 2012; Mouraux et al., 2013; Mouraux et al., 2010). Each participant's detection threshold was determined with single-pulse stimuli (0.5 ms square wave pulse) using a staircase procedure (Churyukanov, Plaghki, Legrain, & Mouraux, 2012). Detection thresholds were established separately for each of the participant's hands. Next, the stimulus intensity was set at twice the detection threshold. If necessary, the intensity of the stimuli were adjusted so that the stimuli delivered to each hand were perceived as being equally intense. During the course of the experiment itself, the stimuli consisted of trains of three consecutive 0.5 ms square-wave pulses separated by a 5-ms inter-pulse interval. This method has been shown to increase the stimulus strength (Inui et al., 2006) without changing the type of activated fibers (Mouraux, Marot, & Legrain, 2014). Using a selection of pain words from the Dutch McGill Pain questionnaire (Vanderiet, Adriaensen, Carton, & Vertommen, 1987), it was found that the experience of the stimuli was best described as pricking and slightly unpleasant (see also Colon, Nozaradan, Legrain, & Mouraux, 2012; Favril, Mouraux, Sambo, & Legrain, in press; Inui et al., 2006; Mouraux et al., 2010). After each experimental block, the participants were asked to estimate the intensity elicited by the nociceptive stimuli on a 10-point VAS scale (0 = not intense (felt nothing), 10 = very intense) in order to ensure that (1) the stimuli were still perceived, and (2) the percept elicited by the IES delivered to each of the participant's hands was still equivalent. If one of these two criteria was not met, the stimulus intensities were modified accordingly. If the adaptation proved to be unsuccessful, the electrodes were displaced and the procedure was restarted.

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

The participants sat on a chair in a dimly illuminated, sound-attenuated room. They rested their arms on the table in front of them. The participants placed their

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