Remapping nociceptive stimuli into a peripersonal reference frame is spatially locked to the stimulated limb.

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Abstract

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

1. Introduction

The ability to localize somatosensory stimuli on the body is important to identify the impact of an external object on the body surface. It is also important to adapt purposeful behavior to that object, such as manipulation behaviors in the case of tactile inputs from a non-harmful object and protective behaviors in the case of nociceptive inputs from a potentially harmful object (Haggard, Iannetti, & Longo, 2013; Legrain & Torta, 2015). The execution of adaptive behaviors towards objects approaching the body requires coordinating reference frames coding the body space with those coding external space. The peripersonal frames of reference are coordinate systems integrating representations of the body space and the external space closely surrounding the body (Cardinali, Brozzoli, & Farnè, 2009; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981; Spence & Driver, 2004) and within this space the location of somatosensory stimuli, the location of visual stimuli occurring close to the body and information about body posture are integrated. Animal studies suggest that such integrated spatial representations rely on neurons with multimodal receptive fields (RFs), mainly in the ventral parts of the premotor and intraparietal areas (Avillac, Denève, Olivier, Pouget, & Duhamel, 2005; Graziano, Hu, & Gross, 1997; Graziano, Yap, & Gross, 1994). More specifically, these neurons have been shown to be active in response to both tactile stimuli and visual stimuli occurring close to the stimulated body parts (Fogassi et al., 1996; Graziano et al., 1997). The visual RFs of these neurons are limited in size and are spatially locked to the tactile RFs, in the sense that these visual RFs follow the movements of the limb to which they are anchored in external space, independently of the retinal representation of the visual inputs. Dong et al. (1994) found similar multimodal neurons in area 7b in the inferior parietal lobe of monkeys. These neurons respond both to thermal nociceptive stimuli and to dynamical visual stimuli moving towards the RF of neurons or static visual stimuli presented in vicinity of the somatosensory RF.

Also in humans there is evidence for the use of peripersonal frames of reference for the localization of somatosensory stimuli. For the mapping of tactile stimuli, several studies have shown that

crossmodal interactions between external (e.g. visual) stimuli and tactile stimuli are more efficient when the visual stimuli are presented close to the limb on which the tactile stimuli are applied, as compared to when they are presented further away (for a review, see Spence & Driver, 2004). For example, Làdavas, di Pellegrino, Farnè, & Zeloni (1998) have shown that, in patients with brain lesions affecting various areas of the right hemisphere, the perception of a tactile stimulus applied to the hand contralateral to the lesion side is affected by the occurrence of a concomitant tactile stimulus applied to the opposite hand. Interestingly, such “extinction” phenomenon also occurs when a concomitant visual stimulus is applied to the opposite side, but only when that stimulus appears in the space near the opposite hand. Conversely, extinction is not observed when visual stimuli are presented far from the opposite hand or close to another body part (Làdavas et al., 1998). Recently, we extended these results to nociceptive stimuli. To this end, we used temporal order judgment (TOJ) tasks during which participants had to judge which of two nociceptive stimuli, one applied to each hand, was perceived as first delivered. Two pairs of light emitting diodes (LEDs) were placed on the horizontal plane, one pair close to the stimulated hands, the second pair further away, according the anteroposterior axis. When a visual stimulus was presented only in one of the two sides, nociceptive order judgments were biased in favor of the nociceptive stimulus applied to the hand ipsilateral to the visual stimulus. Importantly, this effect was largest when the visual stimulus appeared in close proximity of the stimulated hand, as opposed to when presented at the far position (De Paepe, Crombez, Spence, & Legrain, 2014). Moreover, in a subsequent series of experiments, participants were required to perform the same task both in normal posture, and with hands crossed over the sagittal body midline (De Paepe, Crombez, & Legrain, 2015). Results showed that visual stimuli prioritized the perception of nociceptive stimuli applied to the hand lying in the side of space where the visual stimulus was presented, irrespective of posture, providing evidence that processing nociceptive inputs uses space-based frames of reference, according to which the body posture is taken into account. Similar results were observed by Rossetti, Romano, Bolognini & Maravita (2014) who investigated the impact of

approaching threatening stimuli on vegetative responses such as the skin conductance response (SCR) and showed that SCR was greater when the threatening stimulus was close to the body as compared to when it was far.

Unlike studies in monkeys (Fogassi et al., 1996; Graziano et al., 1997), studies investigating the mapping of nociceptive stimuli in a peripersonal frame of reference in humans have mainly focused on a representation of the peripersonal space of the whole body using the body's main axes, such as the midsagittal plane, splitting the body into two hemisides. Indeed, in the above mentioned studies either the position of the visual stimuli (De Paepe et al., 2014) or the position of the hands (De Paepe et al., 2015) was manipulated, leaving us unable to conclude whether the crossmodal interaction between visual and nociceptive stimuli is most effective in a spatial representation of the whole body or of the stimulated body part itself. Here we hypothesized that such interaction takes place in a perilimb spatial representation. Our hypothesis was tested using TOJ tasks with pairs of nociceptive stimuli applied to each hand, preceded by one visual stimulus presented either in the left or the right side of space. Crucially, the position of both the stimulated hand and the visual stimulus was manipulated so that the visual and the nociceptive stimuli occurred either at a close adjacent position or at a certain distance from each other, independently of their relative proximity from the body. Across blocks of stimulation, hands and visual lights were displaced according to the anteroposterior axis (i.e. in depth in front of the trunk, Experiment 1), the mediolateral axis (i.e. eccentricity relative to the body midline, Experiment 2), and the longitudinal axis (i.e. according to elevation positions, Experiment 3). We expected participants' judgments to be biased toward the side of space where the visual stimulus is presented and more importantly we expected this bias to be larger when the locations of the visual stimuli and the stimulated hands were congruent, irrespective of the relative distance of both the hands and the visual stimuli from the body as a whole.

2. Method

2.1. Participants

For each experiment, we aimed for a sample size of approximately 25 participants, in order to keep at least 20 participants for data-analysis. Depending on the availability of participants, and the cancellation of appointments, sample sizes varied across experiments. All participants had normal, or corrected-to-normal vision, did not report any neurological, psychiatric, upper limb trauma or chronic pain problems, and were currently not using any psychotropic and analgesic drugs, which were exclusion criteria. All participants were naïve to the purpose of the experiment, and did not participate before in any experiment on crossmodal interactions in the peripersonal space. Participants could only take part in one of the three experiments of the present study. The experimental procedure was approved by the local ethics committee. All of the participants provided written informed consent prior to taking part in the study.

2.1.1. Experiment 1

Twenty-six participants volunteered to take part in the study. Two male participants had to stop the experiment during the first block, because they were not able to feel the nociceptive stimuli despite repeated displacement of the electrodes (see section 2.2.). The mean age of the remaining 24 participants (20 female, 22 right-handed) was 23 years (ranging from 19 to 47 years).

2.1.2. Experiment 2

Twenty-two participants volunteered to take part in the study. The mean age of the participants (18 women, 20 right-handed) was 23 years (ranging from 18 to 29 years).

2.1.3. Experiment 3

Twenty-five participants volunteered to take part in the study. One participant was excluded due to the use of antidepressant medication at the time of the experiment. Another participant was

excluded due to technical failure. The mean age of the remaining 23 participants (15 women, 20 right-handed) was 22 years (ranging from 18 to 26 years).

2.2. Stimuli and apparatus

The nociceptive stimuli were delivered by means of intra-epidermal electrical stimulation (IES) (DS7 Stimulator, Digitimer Ltd, UK), with stainless steel concentric bipolar electrodes (Nihon Kohden, Japan; Inui, Tsuji, & Kakigi, 2006). The electrodes consisted of a needle cathode (length: 0.1 mm, $\emptyset$: 0.2 mm) surrounded by a cylindrical anode ($\emptyset$: 1.4 mm). By gently pressing the device against the participant's skin, the needle electrode was inserted into the epidermis of the dorsum of the hand in the sensory territory of the superficial branch of the radial nerve. Using IES at maximum twice the absolute detection threshold has been shown previously to selectively activate the free nerve endings of the A δ fibers (Mouraux, Iannetti, & Plaghki, 2010). The detection threshold was determined with a staircase procedure using single-pulse stimuli (0.5 ms square wave pulse) (Churyukanov, Plaghki, Legrain, & Mouraux, 2012). The intensity of the electrical currents were adapted individually, that is, increased or decreased in steps of 0.10 mA, depending on whether the participant reported having perceived the preceding stimulus. The staircase ended after four reversals in intensity direction. Threshold was defined as the mean of intensities at the four reversal levels. The detection threshold was established separately for each hand. Next, the stimulus intensity was set at twice the detection threshold. If necessary, the intensity of the stimuli was adjusted so that the stimuli delivered to each hand were perceived as being equally intense. During the course of the experiment, the stimuli consisted of trains of four consecutive 0.5 ms square-wave pulses separated by a 5-ms inter-pulse interval (Mouraux, Marot, & Legrain, 2014). Using a set of pain words from the Dutch McGill Pain questionnaire (Vanderiet, Adriaensen, Carton, & Vertommen, 1987), the stimuli have been found to be best described as pricking. After each experimental block, the participants were asked to estimate the intensity elicited by the nociceptive stimuli on a numerical graphic rating scale (10 cm) with the following labels selected from the Dutch McGill Pain questionnaire (Vanderiet et al., 1987): 0 = felt

nothing, 2.5 = lightly intense, 5 = moderately intense, 7.5 = very intense, 10 = enormously intense. This scale was used in order to ensure that: (1) the stimuli were still perceived, and (2) the percept elicited by the IES delivered to each of the participant's hands was still equivalent. If one of these criteria was not met, the stimulus intensities were modified accordingly (with a maximum increase in intensity of 0.10 mA). When this adaptation proved to be unsuccessful (i.e. one of the criteria was still not met), the electrodes were displaced and the procedure was restarted.

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

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

Responses were given by two foot pedals, one positioned under the toes, and one under the heel. Participants were instructed to keep the foot pedals pressed down, and to either raise their heel or their toes briefly to respond which hand was stimulated first. Half of the participants responded with their left foot, the other half with their right foot. The response mapping (toe = left hand, heel = right hand, or vice versa) was counterbalanced between participants. Participants were instructed to be as accurate as possible. Speed was not important. To mask any noise produced by the foot pedals, participants wore headphones (WESC, Conga) through which white noise was presented (42.2 dB). By using a 'toe versus heel' response instead of a 'left versus right' response, we aim at minimizing response bias caused by a tendency of participants to respond with the side on which the unilateral cue had been presented (Filbrich, Torta, Vanderclausen, Azañón, & Legrain, 2016).

2.3. Procedure

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

Thereafter, the actual experiment started.

2.3.1. Experiment 1

The experiment consisted of 8 blocks of 60 trials. 35 cm in front of the participants' trunk, on the line extending the body midline, a red fixation LED was attached to the table (Figure 1). Participants were asked to keep their gaze on this fixation LED throughout the experiment. Four green LEDs were positioned relative to the anteroposterior axis, in front of the participants. Two LEDs were positioned at a proximal position relative to the participants' body, and two LEDs were positioned at a distal position. The proximal LEDs were placed 20 cm from the line extending the midline of the body, 40 cm apart from each other. The LEDs far from the body were positioned 50 cm in front of the midline of the body, and 30 cm in front of the near LEDs. In four blocks, the proximal LEDs were illuminated, and in the other four blocks the distal LEDs were illuminated. The position of the participants' hands was also manipulated: in half of the blocks, participants were asked to lay their hands on the table in front of them so that the near LEDs were between their thumb and index finger. In the other half of the blocks, they were asked to lay their hands on the table in front of them so that the far LEDs were between their thumb and index finger. In both cases the hands were approximately 40 cm apart. In the blocks during which hands were next to the proximal LEDs, the hands were 20 cm in front of the

participants' trunk, while in the blocks with hands next to distal LEDs, the hands were 50 cm in front of the trunk. By crossing the position of the hands with the position of the LEDs, four different experimental conditions could be distinguished: if the proximal LEDs were illuminated, hands could be placed at a congruent position with respect to the LEDs, i.e. at the proximal position (two blocks), or at an incongruent position, i.e. next to the LEDs that were actually not used for visual stimulation during these blocks (distal LEDs, two blocks), and vice versa when the distal LEDs were illuminated.

2.2.2. Experiment 2

The experiment consisted of 8 blocks of 60 trials. 40 cm in front of the participants' trunk, on the line extending the body midline, a red fixation LED was attached to the table (Figure 1). Participants were asked to keep their gaze on this fixation LED throughout the experiment. Twenty cm to the left and the right of fixation, two green LEDs were attached to the table (medial position relative to the mediolateral axis). Two other green LEDs were attached to the table at a horizontal distance of 50 cm to the left and right of the fixation LED (lateral position), and at a horizontal distance of 30 cm from the medial LEDs. The position of the participants' hands was manipulated: in half of the blocks they were asked to rest their arms on the table in front of them so that the medial LEDs were between the thumb and index finger of their hands. In the other half of the blocks they were asked to rest their arms on the table in front of them so that the lateral LEDs were between the thumb and index finger of their hands. In the former case the hands were 40 cm apart. In the latter case, the hands were 100 cm apart. In both cases the hands were positioned 40 cm in front of the trunk. Four different experimental conditions were created, similarly to Experiment 1.

2.2.3. Experiment 3

The experiment consisted of four blocks of 120 trials. Participants were sitting in front of a black 50-cm-high curved screen that was positioned vertically at 40 cm from the participants' trunk and about 5 cm above the table (Figure 1). Four green LEDs were attached to the screen. Two of the LEDs were positioned at the bottom of the screen, 40 cm apart from each other (low position relative to the longitudinal axis of the body). The two other LEDs were attached at the top of the screen, 50 cm above the low cues (high position). Participants stretched their hands beneath the screen so that the index finger of their left and right hand were positioned underneath the left and right (low) LEDs respectively. Participants were fixating on a red LED that was attached to the screen at a position equidistantly from the low and high LEDs (25 cm above or below the green LEDs), and equidistantly from the left and right LEDs (20 cm to the left or right of the green LEDs). Participants were sitting so that the red fixation LEDs was positioned on the line extending the midline of the participants' body (therefore left and right green LEDs were equidistant from the body midline). In two blocks visual stimuli were presented using the low LEDs. In the other two blocks they were presented using the high LEDs. Therefore the position of the visual stimulus was congruent with respect to hand position during the blocks with low visual stimulus position, and incongruent during the blocks with high visual stimulus position. The order of the blocks was alternated and counterbalanced across participants.

Figure 1. Left panel. Experimental set-up Experiment 1. Visual stimulus position was manipulated according the anteroposterior axis, and hands were positioned at a congruent or incongruent position. **Middle panel. Experimental set-up Experiment 2.** Visual stimulus position was manipulated according the mediolateral axis, and hands were positioned at a congruent or incongruent position. **Right panel. Experimental set-up Experiment 3.** Visual stimulus position was manipulated according the longitudinal axis, so that the visual stimulus was either at a congruent or incongruent position with respect to the hands.

In the three experiments, a trial started with the red fixation LED being illuminated. This fixation LED stayed on during the entire trial. 500 ms after the onset of the fixation LED, the visual stimulus was flashed during 20 ms, using the LED from either the left or the right side of space. Probability of occurrence was equivalent for left and right visual stimuli. The visual stimulus was followed 80 ms later by a pair of nociceptive stimuli, one applied to either hand. The first nociceptive stimulus could be applied either to the left or the right hand. Five possible stimulus onset asynchronies (SOAs) were used between the two nociceptive stimuli for each order of stimulation (left hand first vs. right hand first): ± 200 , ± 90 , ± 55 , ± 30 , ± 10 ms (where positive values indicate that the participant's right hand was stimulated first, and negative values indicate that their left hand was stimulated first). The trials were created combining 2 spatial locations of the visual stimuli x 2 orders for the nociceptive stimuli

x 5 SOAs. Trials were randomly presented within each block of stimulation. The visual cues were spatially uninformative, and the location of any forthcoming nociceptive stimulus could thus not be predicted by the cue.

Participants were instructed to keep their gaze on the red fixation LED throughout each block of trials and to indicate by means of the foot pedals, which hand was stimulated first. After the participants had made their response, the fixation LED was turned off. If participants did not respond within 10s, the fixation LED flickered 3 times before the experiment continued. After 1000 ms, the next trial started. The experiments took approximately 60 minutes.

2.4. Measures

The procedure followed was the same for the three experiments and is similar to the one reported in Spence, Shore, & Klein (2001) (see also De Paepe et al., 2015, 2014; Van Damme, Gallace, Spence, Crombez, & Moseley, 2009). For each participant, and for each SOA for the two or four within-participant conditions (in Experiment 1: proximal vs. distal visual stimulus position x congruent vs. incongruent hand position; in Experiment 2: medial vs. lateral visual stimulus position x congruent vs. incongruent hand position; in Experiment 3: congruent vs. incongruent visual stimulus position), the proportion of trials on which participants perceived the left/right hand as being stimulated first (i.e., the left hand if visual cue stimuli were presented in the left side of space and the right hand if visual stimuli were presented in the right side of space) was calculated. A sigmoid function was fitted to these proportions (see Figure 2). Subsequently, the proportion of *left/right hand first responses* was converted into z-scores by means of a standardized cumulative normal distribution (probits). The best-fitting straight line was computed for each participant and each condition, and the derived slope

284 and intercept values were used to compute the point of subjective simultaneity (PSS)¹. The PSS refers
285 to the point at which participants report the two events (i.e., the nociceptive stimulus presented to
286 the cued hand and the nociceptive stimulus to the uncued hand, that is, the hand contralateral to the
287 visual stimulus) as occurring first equally often. This is equivalent to the SOA value corresponding to
288 a proportion of *left/right hand first responses* of 0.5 (Spence et al., 2001). The PSS is computed as the
289 opposite of the intercept divided by the slope from the best-fitting straight line. The sign of the PSS
290 for the conditions in which the cues were presented on the right side of space was reversed and for
291 each participant the final PSS value was calculated by taking the average of the PSS values for cues
292 presented in the left side of space and the reversed value for cues presented in the right side of space.
293 Therefore, the PSS reflects how much time the nociceptive stimulus at the uncued hand had to be
294 presented before/after the cued hand in order to be perceived as having occurred at the same time.
295 In sum, the PSS provides information concerning biases in spatial attention resulting from the
296 presentation of the visual stimuli.

¹ Another measure often used in TOJ tasks is the just noticeable difference (JND), which provides a standardized measure of the sensitivity of participants' temporal perception. However, as we were interested in the attentional bias induced by the cues, which is reflected by the PSS, we did not take the JND into account here for the sake of parsimony. Data are available in the supplementary information (S1 file).

Figure 2. Left panel. Nociceptive temporal order judgments (TOJs) for Experiment 1. The figure illustrates the fitted curves from cumulative data from 24 participants. Trials were either associated with visual stimuli at a proximal position (upper figure) or at a distal position (lower figure), and with hands on the congruent positions (blue solid line) or hands on the incongruent positions (red dotted line). Data are plotted as the mean proportion of *cued hand first responses* (on the Y-axis), as a function of the stimulus onset asynchronies (SOA) (on the X-axis). On the X-axis, negative values indicate that the cued hand was stimulated first, while positive values indicate that the uncued hand was stimulated first. The vertical dashed lines coincide with the PSS values. All curves were shifted toward the uncued side, indicating that the nociceptive stimulus on the uncued hand had to be presented several milliseconds before the stimulus on the cued hand to have an equal chance to be perceived first. Importantly, this bias was larger when hand position was congruent to the visual stimulus position, irrespective of the distance of the visual stimulus to the body trunk. **Middle panel. Nociceptive temporal order judgments (TOJs) for Experiment 2.** The figure illustrates the fitted curves from cumulative data from 22 participants. Trials were either associated with visual stimuli at a medial (upper figure) or at a lateral position (lower figure), and with hands on the congruent (blue solid line) or the incongruent positions (red dotted line). Data are plotted as the mean proportion of *cued hand first responses* (on the Y-axis), as a function of the stimulus onset asynchronies (SOA) (on the X-axis). On the X-axis, negative values indicate that the cued hand was stimulated first, while positive values indicate that the uncued hand was stimulated first. The vertical dashed lines coincide with the PSS values. All curves were shifted toward the uncued side,

indicating that the nociceptive stimulus on the uncued hand had to be presented several milliseconds before the stimulus on the cued hand to have an equal chance to be perceived first. Importantly, this bias was larger when hand position was congruent to the visual stimulus position. Moreover, the difference in PSS values between the congruent and the incongruent hand position was larger when visual stimuli were presented medial as opposed to lateral. **Right panel. Nociceptive temporal order judgments (TOJs) for Experiment 3.** The figure illustrates the fitted curves from cumulative data from 23 participants. Trials were either associated with visual stimuli at a congruent (blue solid line) or an incongruent position (dashed red line). Data are plotted as the mean proportion of *cued hand first responses* (on the Y-axis), as a function of the stimulus onset asynchronies (SOA) (on the X-axis). On the X-axis, negative values indicate that the cued hand was stimulated first, while positive values indicate that the uncued hand was stimulated first. The vertical dashed lines coincide with the PSS values. All curves were shifted toward the uncued side, indicating that the nociceptive stimulus on the uncued hand had to be presented several milliseconds before the stimulus on the cued hand to have an equal chance to be perceived first. Importantly, this bias was larger when visual stimulus position was congruent as opposed to incongruent to the hands. As the distance of the visual stimuli to the body trunk was kept constant, it is unlikely that this influenced results.

2.5. Analyses

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

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

Next, in order to compare the PSS values across the different conditions, results were analyzed using the linear mixed effects models as implemented in the R package “Linear and Nonlinear Mixed Effects Models” (Pinheiro & Bates, 2000). Linear mixed effect models 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, & Galecki, 2007, for an elaboration). We chose to analyze the data with linear mixed models because it is a more subject-specific model and it allows unbalanced data, unlike the classical general linear models which require a completely balanced array of data (West et al., 2007).

The outcome variable was the PSS. The independent variables were the visual stimulus position (Experiment 1: proximal vs. distal; Experiment 2: medial vs. lateral; Experiment 3: low (congruent) vs. high (incongruent)) and, only in Experiments 1 and 2, the congruency of the hand position relative to the visual stimuli (congruent vs. incongruent). These were manipulated within subjects. Each analysis required three steps. First, all relevant factors and interactions were entered in the model as fixed factors, and we assessed whether it was necessary to add a random effect for each of the fixed factors in the analysis: if a random effect significantly increased the fit of the model, it was included in the final model. By default, a random effect was added introducing adjustments to the intercept conditional on the Subject variable. In the second step, we searched for the most parsimonious model that fitted the data. To achieve this, we systematically restricted the full model, comparing the goodness of fit using likelihood-ratio tests. Finally, in the third step, we inspected the ANOVA table of the final model and tested specific hypotheses about possible main effects or interactions (for a similar approach see De Paepe et al., 2015; De Ruddere et al., 2011; Verbruggen, Aron, Stevens, & Chambers, 2010). Kenward-Roger approximations to the degrees of freedom were used to adjust for small sample sizes (Kenward & Roger, 1997). When an interaction effect was significant, it was further investigated with follow-up contrast analyses, corrected for multiple testing according to the Holm-Bonferroni corrections (Holm, 1979). Standardized regression coefficients were reported as a measure of the effect size. The different steps in the model building procedure are illustrated in the Appendix (Table A1 to A7).

3. Results

3.1. Intensity of the nociceptive stimuli

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

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

3.2. Missing values

In Experiment 1, 4 out of 96 (4 conditions x 24 participants; 4.00%) values were excluded, because the PSS exceeded twice the maximum SOA; all of these were from a condition where hands were on the congruent position. A chi-squared test indicated that the proportion missing values was not significantly different between the congruent and the incongruent hand position conditions ($\chi^2(1,96) = 2.35$; $p = 0.13$). In Experiment 2, no values were excluded. Finally, in Experiment 3, 3 out of 46 (2 conditions x 23 participants; 6.52%) values were excluded, because the PSS exceeded twice the maximum SOA; all of these were from the blocks with visual stimuli at the congruent position. A chi-

squared test indicated that the proportion missing values was not significantly different between the visual stimuli at congruent and those at incongruent positions ($\chi^2(1,46) = 1.43; p = 0.23$).

3.3. PSS

3.3.1. Experiment 1

The t-test revealed that the PSS values were significantly different from 0 in all 4 conditions (proximal visual stimuli, hands at congruent position ($M = 97.44; SD = 72.15$): $t(21) = 6.33; p < 0.001$; proximal visual stimuli, hands at incongruent position ($M = 17.94; SD = 32.95$): $t(23) = 2.67, p = 0.01$; distal visual stimuli, hands at congruent position ($M = 104.56; SD = 72.18$): $t(21) = 6.79, p < 0.001$; distal visual stimuli, hands at incongruent position ($M = 40.87; SD = 55.06$): $t(23) = 3.64, p = 0.001$). This indicates that the PSS was biased by the presence of lateralized visual stimuli. The linear mixed effects model that demonstrated the best fit with the data, included the fixed factors (*visual stimuli position* and *hand congruency*), a random subject-based intercept and a random effect for *hand congruency*. Adding the interaction effect between the fixed factors did not significantly improve the model. The interaction effect was therefore not included in the model. In this final model, there was a main effect of *hand congruency* ($F(1,21.01) = 34.15; p < 0.001; \beta = -0.55$), indicating that PSS values were more positive when the position was congruent to the position of the visual stimuli, as compared to trials when visual stimuli and hand positions were incongruent. The main effect of *visual stimulus position* was not significant ($F(1,45) = 3.05; p = 0.09; \beta = -0.11$). These results indicate that the relative position of the visual stimuli to the stimulated body part had an influence on nociceptive processing, rather than the distance of the visual stimuli to the trunk (Figure 3).

3.3.2. Experiment 2

The t-test revealed that the PSS values were significantly different from 0 in all 4 conditions (medial visual stimuli, hands at congruent position ($M = 155.56$; $SD = 103.48$): $t(21) = 7.05$; $p < 0.001$; medial visual stimuli, hands at incongruent position ($M = 77.11$; $SD = 57.51$): $t(21) = 6.29$, $p < 0.001$; lateral visual stimuli, hands at congruent position ($M = 79.98$; $SD = 71.11$): $t(21) = 5.28$, $p < 0.001$; lateral visual stimuli, hands at incongruent position ($M = 44.99$; $SD = 39.61$): $t(21) = 5.33$, $p < 0.001$). This indicates that the PSS was biased by the presence of lateralized visual stimuli. The linear mixed effects model that demonstrated the best fit with the data, included the fixed factors (*visual stimulus position* and *hand congruency*) as well as their interaction, a random subject-based intercept, and a random effect for *visual stimulus position* and *hand congruency*. In this final model, there was a main effect of *visual stimulus position* ($F(1,34.68) = 35.71$; $p < 0.001$; $\beta = 0.46$), a main effect of *hand congruency* ($F(1,30.47) = 5.45$; $p = 0.03$; $\beta = -0.22$), and an interaction effect between these two factors ($F(1,21) = 10.92$; $p = 0.003$; $\beta = -0.60$). Follow-up t-tests indicated that PSS values were overall higher for visual stimuli at the medial position, and in particular when hands were at the congruent position. This is illustrated by significantly higher PSS values for visual stimuli at the medial than at the lateral position (all $t > -4$, all $p < 0.001$), and significantly higher PSS values when hands were positioned at a congruent than at an incongruent position, especially when visual stimuli were presented at the medial positions ($t(21) = -3.76$; $p < 0.001$), but also, although to a lesser extent, when visual stimuli were presented at the lateral positions ($t(21) = -1.89$, $p = 0.04$). These results suggest that the relative distance between the visual stimuli and the stimulated body part had an influence on nociceptive processing over and above the influence of the distance of the visual stimuli to the body trunk (Figure 3).

3.3.3. Experiment 3

The t-test revealed that the PSS values were significantly different from 0 both when the visual stimuli were presented at the congruent position ($M = 79.78$; $SD = 75.89$) ($t(19) = 4.70$; $p < 0.001$) and

at the incongruent position ($M = 35.45$; $SD = 55.97$) ($t(22) = 3.04$; $p = 0.006$). This indicates that the PSS was biased by the presence of lateralized visual stimuli. The linear mixed effects model that demonstrated the best fit with the data, included the fixed factor (*visual stimulus position*), and a random subject-based intercept. In this final model, there was a significant effect of *visual stimulus position* ($F(1,20.29) = 10.65$; $p = 0.004$; $\beta = 0.36$), indicating that the PSS was more positive with visual stimuli at the congruent position than at the incongruent position (Figure 3).

Figure 3. Left panel. Means and standard errors for the point of subjective simultaneity (PSS) for Experiment 1. Significant differences are indicated with an asterisk ($p < 0.05$). **Middle panel. Means and standard errors for the point of subjective simultaneity (PSS) for Experiment 2.** Significant differences are indicated with an asterisk ($p < 0.05$). **Right panel. Means and standard errors for the point of subjective simultaneity (PSS) for Experiment 3.** Significant differences are indicated with an asterisk ($p < 0.05$).

4. Discussion

In the present experiments, we investigated whether the interactions between visual and nociceptive stimuli (see De Paepe et al., 2015, 2014) are taking place in peripersonal representations of the whole body centered around the main bodily axes (e.g. the midsagittal plane), or representations of each body limb individually. Three experiments were conducted in which we examined the ability to locate nociceptive stimuli by studying the perceived temporal order of two nociceptive stimuli, one to each hand. Before the first nociceptive stimulation, an unilateral visual stimulus was presented. Crucially, the relative position between the hands and the LEDs used to present the visual stimuli was manipulated. We found that the influence of the visual stimuli on nociceptive judgments was most efficient when the stimulated hand was positioned in proximity of the visual stimuli, irrespective of the position of both the stimulated hands and the visual stimuli relative to the trunk (i.e., irrespective from a *whole body* reference). These results provide evidence that nociceptive and visual stimuli interact most strongly within a spatial representation of the stimulated limb itself.

In previous studies, we used TOJ tasks in which two pairs of LEDs were placed on the horizontal plane, one pair close to the stimulated hands, the second pair further away, according the anteroposterior axis (De Paepe et al., 2014). In the present series of experiments, participants placed their hands at different positions. In Experiment 1, participants were required to place their hands more distally, that is, close to the farthest visual stimuli. Results were reversed: nociceptive judgments were now mostly influenced by the distal visual stimuli (the ones closest to the hands), whereas the influence of the visual stimuli at the proximal position was attenuated. This suggests that the crucial feature for crossmodal influence on nociceptive processing is the proximity of the visual stimuli to the body part on which the nociceptive stimuli were applied, and less the proximity to the trunk. Results were corroborated in two further experiments using the other body planes and axes as a reference, so that the positions of the hands and the visual stimuli were manipulated in three-

dimensional space. In Experiment 2, the position of the visual stimuli was manipulated according the mediolateral axis. Overall, results were the same as in Experiment 1, albeit that the effect of the relative distance between the stimulated hand and the visual stimulus was less pronounced when visual stimuli were presented in the lateral position. This may indicate that the overall distance from the trunk can also have an influence on nociceptive processing. Alternatively, this result could be explained by the fact that the lateral position was the most eccentric position relative to the fovea in the three experiments of the present studies. Therefore the relative distance between the hands and the visual stimuli could be more difficult to perceive when the mediolateral axis was manipulated. Results from Experiment 3 were limited by the fact that hand position was not manipulated due to the uncomfortable body posture when the hands were at the high position. However, it is noteworthy that the gaze was directed toward a fixation LED positioned equidistantly from each of the four experimental LEDs. Therefore visual acuity is unlikely to explain the present results.

The results of the present experiments indicate that the ability to locate a nociceptive stimulus on the skin surface uses mapping systems that extend the representation of the body space in external space (i.e., peripersonal representation) with a coordinate reference system centered on each body part and more specifically, in the present studies, on each hand. The distance to the trunk played a minor role, suggesting that these perihand space representations are locked to their referential limb and move with them in space. These results are in line with studies investigating the modular organization of the peripersonal space in monkeys (e.g. Fogassi et al., 1996; Graziano & Gross, 1993). In monkeys several brain areas, in premotor area and the intraparietal sulcus, encode a multisensory map of space centered around a specific body part, (Avillac et al., 2005; Graziano & Gross, 1995; Graziano et al., 1994). In these areas many neurons respond both to the somatosensory stimulation of a specific body part and to visual stimuli that occur close to that body part (Graziano & Gross, 1995; Graziano et al., 1997, 1994). Interestingly, the region of space within which visual stimuli are effective

in exciting these bimodal neurons is modulated by the position of the arms in space (e.g. Fogassi et al., 1996; Graziano et al., 1997, 1994).

In humans similar changes in cross-modal visuo-tactile effects after tool-use are documented (Farnè, Serino, & Làdavas, 2007; Maravita, Spence, & Driver, 2003; Pavani, Spence, & Driver, 2000; Spence, Pavani, & Driver, 2004). Moreover neuropsychological evidence in patients suffering from left tactile extinction following right hemisphere damage suggests that the visuotactile peripersonal space is represented in limb-centered coordinates (di Pellegrino, Làdavas, & Farnè, 1997; Mattingley, Driver, Beschin, & Robertson, 1997). Interestingly, extinction also occurs when a visual stimulus is presented near the ipsilesional hand, but not when it is presented at a certain distance from the hand (di Pellegrino et al., 1997; Alessandro Farnè, Demattè, & Làdavas, 2005; Làdavas et al., 1998). When the visual stimulus remained at a constant distance from the trunk, but the relative distance to the hand was increased, the visual stimulus extinguished the perception of the tactile stimulus applied to the opposite hand only to a lesser extent (di Pellegrino et al., 1997; Làdavas et al., 1998). Finally, Farnè, Demattè, & Làdavas (2005) have shown that a tactile stimulus applied to the left hand can be extinguished by a visual stimulus delivered close to the right hand, but not close to the right cheek. The reverse was observed for tactile stimuli applied to the right cheek. This suggests that crossmodal extinction observed in those studies results from the competition between the representations of two opposite but homologous body parts.

In the present paper we were able to extend the results mentioned above to nociceptive processing in healthy volunteers. The ability to localize nociceptive stimuli is important, because it enables us to detect which part of the body is damaged, and to react against potential physical threats. The existence of a peripersonal frame of reference for the localization of nociceptive stimuli implies that nociceptive inputs are integrated in a multisensory system that monitors the space immediately surrounding our body and detects any sensory information having a potential impact on our body. Therefore the coding of nociceptive information in a peripersonal frame of reference may constitute

a safety margin around the body that protects it from potential physical threats and represents a mechanism for preserving homeostatic control over the body (Moseley, Gallace, & Iannetti, 2012). Here we were able to show that this peripersonal representation can be limited to the limb on which the nociceptive stimulus is applied. This implies that the mere proximity to the trunk might not be sufficient for an external stimulus to be integrated in the peripersonal space. Instead this stimulus must be near the body part that is currently stimulated. Crucially, we showed that these perilimb representations are anchored to the limb they code and are displaced with it in space. This would allow giving priority to stimuli around that limb. Nevertheless, this interpretation does not exclude the possibility that the distance of stimuli to the trunk also plays a role in the representation of peripersonal space, as suggested by the results of Experiment 2. Analogously, Rossetti et al. (2014) found that pain anticipatory responses were greater when threatening stimuli were approaching the hand along the vertical axis as opposed to the horizontal axis. The authors suggest that this might be due to the fact that stimuli delivered along this axis were also closer to the head and the trunk, stressing the importance of the distance to the trunk. However, overall results of our experiments indicate that hand-centered space has a stronger impact on nociceptive processing than trunk-centered space.

Our results highlight the importance of spatial perception to understand the processing of pain. Moreover, it may shed light on the pathophysiology and treatment of chronic pain, as some pain conditions (e.g. complex regional pain syndrome) are associated with cognitive deficits altering the ability to represent and perceive the body and the surrounding space (for a review see, Legrain, Bultitude, De Paepe, & Rossetti, 2012; Legrain & Torta, 2015). These patients tend to ignore or have an altered representation of the affected limb, and movements are less frequent and smaller (Frettlöh, Hüppe, & Maier, 2006; Galer, Butler, & Jensen, 1995; Lewis, Kersten, McCabe, McPherson, & Blake, 2007). Moseley, Gallace, & Spence (2009) were able to show that the deficits in spatial perception observed in CRPS patients are not related to the pathological limb, but rather to the space in which

548 the limb normally resides. Furthermore, other studies showed that manipulating the spatial
549 perception of these patients can alleviate pain (Bultitude & Rafal, 2010; Sumitani et al., 2007). These
550 studies stress the importance of studying spatial perception in the context of pain, and suggest that
551 manipulating the spatial perception could be a potential rehabilitation technique for some chronic
552 pain patients (Legrain & Torta, 2015).

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Conflict of interest statement

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

Author Contributions

All authors contributed to the study concept and the study design. Testing, data collection, data analysis and interpretation were performed by A.L. De Paepe under the supervision of G. Crombez and V. Legrain. A.L. De Paepe drafted the manuscript and G. Crombez and V. Legrain provided critical revisions. All authors approved the final version of the manuscript for submission.

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Appendix

A top-down model building approach was adopted for fitting LME models (Pinheiro & Bates, 2000; West et al., 2007). First, a full model of the fixed effects was used to determine which random effects should be added to the model. The best pattern for the covariance of the residuals was chosen based on Restricted Maximum Likelihood estimation (REML estimation). Then, we determined which fixed effects needed to be included based on Maximum Likelihood estimation (ML estimation). Fixed effects were removed from the model if they didn't significantly improve the fit of the model. Finally, the final model was refitted with REML estimation and the relevant contrasts were calculated. Below, the three fitting steps for each of the fitted models is presented. For each fitted model, Akaike's information Criterion (AIC, Sakamoto, Ishiguro, & Kitagawa, 1986), the χ^2 for the relevant model comparisons, and the corresponding p-values are shown. The final table for each measure shows the Anova table, and the parameter estimates with their corresponding t-values.

Experiment 1

Step 1. Full model. Determine random effects structure.

Model	Test	Random Slope	AIC	Df	χ^2	p-value
1	Initial fit	1	985	6		
2	Random slope visual stimulus position (1 vs. 2)	1 + visual stimulus position	987	8	$\chi^2(2) = 2.06$	0.36
3	Random slope hand congruency (2 vs. 3)	1 + hand congruency	974	8	$\chi^2(2) = 15.10$	<0.001

Table A1. Decision: keep model 3 with random intercept for Subject and random slope for congruency.

Step 2. Determine fixed effects structure.

Model	Test	Fixed	AIC	Df	χ^2	p-value
1	Initial fit	visual stimulus position * hand congruency	1000	8		
2	Remove interaction (1 vs. 2)	visual stimulus position + hand congruency	999	7	$\chi^2(1) = 0.83$	0.36

Table A2. Decision: keep model 2 without the interaction between visual stimulus position and congruency.

Step 3. Test final model.

Effects	F	Df1	Df2	p
visual stimulus position	3.05	1	45.00	0.09
hand congruency	34.15	1	21.01	< 0.001

	B	SE(B)	t	CI
Intercept	113.15	15.02	7.53	[83.71 to 142.58]
visual stimulus position	-15.37	8.80	-1.75	[-32.61 to 1.87]
hand congruency	-76.06	12.97	-5.87	[-101.47 to -50.65]

Table A3. Above: ANOVA table for the final model. Below: Parameter estimates (in ms) and their corresponding standard errors, t- values and confidence intervals.

Experiment 2

Step 1. Full model. Determine random effects structure.

Model	Test	Random Slope	AIC	Df	χ^2	p-value
1	Initial fit	1	955	6		
2	Random slope visual stimulus position (1 vs. 2)	1 + visual stimulus position	953	8	$\chi^2(2) = 5.83$	0.05
3	Random slope visual stimulus position and hand congruency (2 vs. 3)	1 + visual stimulus position + hand congruency	930	11	$\chi^2(3) = 28.82$	<0.001

Table A4. Decision: keep model 3 with random intercept for Subject and random slope for visual stimulus position and congruency.

Step 2. Determine fixed effects structure.

Model	Test	Fixed	AIC	Df	χ^2	<i>p</i> -value
1	Initial fit	visual stimulus position * hand congruency	956	11		
2	Remove interaction (1 vs. 2)	visual stimulus position + hand congruency	964	10	$\chi^2(1) = 9.90$	0.002

Table A5. Decision: keep model 1 with the interaction between visual stimulus position and congruency.

Step 3. Test final model.

Effects	F	Df1	Df2	<i>p</i>
visual stimulus position	35.71	1	34.68	< 0.001
hand congruency	5.45	1	30.47	0.03
visual stimulus position * hand congruency	10.92	1	21.00	0.003

	<i>B</i>	SE(B)	<i>t</i>	CI
Intercept	79.98	16.51	4.84	[47.61 to 112.34]
visual stimulus position	75.58	12.65	5.98	[50.79 to 100.38]
hand congruency	-34.99	14.99	-2.33	[-64.37 to -5.61]
visual stimulus position * hand congruency	-43.45	13.15	-3.30	[-69.23 to -17.67]

Table A6. Above: ANOVA table for the final model. Below: Parameter estimates (in ms) and their corresponding standard errors, *t*- values and confidence intervals.

Experiment 3

By adding a random slope for visual stimulus position, the number of random effects exceeds the number of observations. Therefore, this model cannot be fit and the final model chosen included the fixed factor (*visual stimulus position*), and a random subject-based intercept (AIC = 470).

Step3. Test final model.

Effects	F	Df1	Df2	p
visual stimulus position	10.65	1	20.29	0.004

	B	SE(B)	t	CI
Intercept	35.45	13.81	2.57	[8.37 to 62.52]
cue distance	49.64	15.15	3.28	[19.95 to 79.33]

Table A7. Above: ANOVA table for the final model. Below: Parameter estimates (in ms) and their corresponding standard errors, t- values and confidence intervals.

Supplementary information

Model building procedure, ANOVA tables and bar plots for the JND data for Experiment 1, 2 and 3 are documented in the supplementary information file.