1 **Mapping nociceptive stimuli in a peripersonal frame of reference:**

2 **Evidence from a temporal order judgment task**

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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.

Keywords: peripersonal space, attention, crossmodal integration, temporal order judgment, nociception

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, 2011). 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 & 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 references. For instance, Sambo et al. (2013) and Gallace et al. (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 body limbs) and a spatiotopic representation (defining the position of the stimulated limbs in external space; see Shore, Spry, & Spence, 2002). Similarly, Moseley, Gallace, and Spence (2009) have shown that unilateral chronic pain, such as in complex regional pain syndrome (CRPS), a chronic pain disorder characterized by unilateral sensory, autonomous, vasomotor and motor/trophic dysfunctions, affects the spatiotopic representation of personal space. In other experiments, Sambo et al. (2012a, b) and Sambo

and Iannetti (2013) found 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. *Analyses*). 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 A δ 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 A β -fiber mechanoreceptors, a strict procedure was used to individually adjust the intensity of the stimulus to two times the detection threshold with an electrical current intensity that was as low as possible (Legrain & Mouraux, 2012; Mouraux et al., 2013; Mouraux, Iannetti, & Plaghki, 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, in press). Using a selection of pain words from the Dutch McGill Pain questionnaire (Vanderiet, Adriaensen, Carton, & Vertommen, 1987), it was found that the experience of the stimuli was best described as pricking and slightly unpleasant (see also Colon, Nozaradan, Legrain, & Mouraux, 2012; Favril et al., 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 hands, palm downward, on the table in front of a 16 inch CRT monitor used to present a fixation stimulus. The participant’s head was immobilized in a chin-rest positioned at 10 cm from the trunk, in order to prevent the vision of the hands. The height of the chin-rest was individually adapted. The distance between the participant’s hands and their trunk, as well as the distance between the participant’s index fingers was 40 cm. Two of the LEDs were situated in near/peripersonal space, and two in far/extrapersonal space. The LEDs in near space were placed on the dorsum of the participant’s hands, close to the IES electrodes (the distance between the two LEDs was therefore also approximately 40 cm). To dissociate any effects attributable to the distance of the LEDs from the participant’s body (i.e., peripersonal vs. extrapersonal space) from any effects attributable to the distance of the LEDs from the fixation point, the location of the screen and the LEDs in far space varied across participants (between-participant factor: *fixation distance*). For 11 of the participants, the LEDs in far space and the screen were positioned 100 cm from the participant’s trunk (*far fixation* condition, see Figure 1A). The distance between the two LEDs in far space was 60 cm. For the other 10 participants, the LEDs in far space were positioned 80 cm from the participant’s trunk, and the screen at a

distance of 40 cm, i.e., close to the LEDs in near space (*near fixation* condition, see Figure 1B). The distance between the two LEDs in far space was 70 cm.

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

The first nociceptive stimulus could be applied either to the left hand or the right hand. There were five possible SOAs between the nociceptive stimuli for each order of stimulation (left hand first vs. right hand first): ± 120 , ± 60 , ± 30 , ± 15 , ± 5 ms (where positive values indicate that the participant’s right hand was stimulated first, and negative values indicate that their left hand was stimulated first). The fixation cross remained on-screen until the

participants had responded, whereupon it was replaced by a text prompt to respond (“Provide a response”).

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

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

2.1.4. Measures. The procedure followed that reported in Spence et al. (2001; see also Shore, Gray, Spry, & Spence, 2005; Van Damme, Gallace, Spence, Crombez, & Moseley, 2009). For each participant, and for each SOA for each of the 8 within-participant conditions (bilateral vs. unilateral cues x close vs. far space x which first? vs. which second?), the proportion of trials on which participants perceived the cued hand as being stimulated first, was calculated. A sigmoid function was fitted to these proportions (see Figure 3).

Subsequently, the proportion of *left/right hand first responses* (left hand first when the cue was presented on the left side, and right hands first when cues were presented on the right side) was converted into a z-score by means of a standardized cumulative normal distribution (probits). The best-fitting straight line was computed for each participant and each condition, and the derived slope and intercept values were used to compute the point of subjective simultaneity (PSS) and the just noticeable difference (JND).

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

The JND was measured as $0.675/\text{slope}$ (Spence et al., 2001). This corresponds to the value achieved by subtracting the SOA at which the best fitting line crosses the 0.75 point from the SOA at which the same line crosses the 0.25 point, and dividing this by two) and indicates the

interval needed to achieve 75% correct performance, and, as such, provides a standardized measure of the sensitivity of participant's temporal perception.

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

2.2. Experiment 2

2.2.1. Participants. Thirteen paid volunteers took part in this experiment. One participant was excluded based on the same exclusion criteria as in Experiment 1 (see Section 2.2.4. *Measures and Analyses*). The mean age of the remaining 12 participants (9 females; 11 right-handed) was 22 years (ranging from 18 to 29 years). All of the participants had normal to

corrected-to-normal vision, reported no neurological, psychiatric, or chronic pain problems, and were not currently using psychotropic drugs. The experimental procedure was approved by the local ethics committee. All of the participants provided informed consent prior to taking part in the study.

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

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

2.2.3. Procedure. The practice session contained a block of 12 trials with visual stimuli only in order to ensure correct detection, and 2 blocks of 24 trials with nociceptive stimuli only with the three largest SOAs in order to ensure correct task performance (80% correct response on the maximum SOA). The experiment consisted of 8 blocks of 60 trials. The trial types were not mixed within each block in this experiment, as was the case for Experiment 1. Four blocks contained visual stimuli in near space only, and four blocks contained visual stimuli in far space only. The order in which the blocks were presented was randomized for the first 4 blocks, and the reverse order was used for the remaining 4 blocks. A trial started with the fixation LED being illuminated. This fixation LED stayed on during the entire trial. 500ms after the onset of the fixation LED, a single unilateral visual flash (either on the right or the left side), or paired bilateral visual flashes were presented. The visual stimulus was followed 80 ms later by a pair of nociceptive stimuli, one applied to either hand. Five possible SOAs were used between the two nociceptive stimuli for each order of stimulation: ± 200 , ± 90 , ± 55 , ± 30 , ± 10 ms (positive values indicate that the right hand was stimulated first, negative values indicate that the left hand was stimulated first). As in Experiment 1, each block of trials was made up of 3 positions of the visual stimuli (bilateral, unilateral/left side, unilateral/right side), 2 cue distances (near, far), 2 order of nociceptive stimuli (left hand first, right hand first) and 5 SOAs. The different resulting trials were equiprobable and randomly presented.

The participants were instructed to keep their gaze on the fixation LED and to indicate verbally which hand they perceived as having been stimulated first during four blocks, and which hand they perceived as having been stimulated second in the four other blocks (again with the order alternated over blocks and counterbalanced across participants). After the participants had made their response, the fixation LED was turned off. The verbal responses

were encoded by the experimenter. The next trial started after a delay period of 1000 ms,. The experiment took an average 75 minutes to complete.

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

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

3. Results

Intensity of the nociceptive stimuli. The mean current intensities used during Experiment 1 were 0.92 ± 0.33 mA and 0.87 ± 0.31 mA for the left and right hands respectively. During Experiment 2, the current intensities were 0.79 ± 0.31 mA and 0.69 ± 0.26 mA for left and right hands, respectively. The differences between the left and right hands were not significant (Experiment 1: $t(20) = 0.93$; $p = .36$; Experiment 2: $t(11) = 0.99$; $p = .34$). These values correspond to those used in previous studies that selectively activated the nociceptors (Colon et al., 2012; Favril et al., in press; Inui et al., 2006; Mouraux et al., 2010). The mean self-reported intensities (VAS) were, during Experiment 1, 4.52 ± 1.87 for left hand and 4.59 ± 1.79 for right hand, and, during Experiment 2, 3.89 ± 1.41 for left hand and for right hand 3.80 ± 1.34 . These differences were also not significant (Experiment 1: $t(20) = -0.72$; $p = .48$; Experiment 2: $t(11) = .79$; $p = .45$).

PSS. Mean responses and mean PSS values are shown in Figure 3 and 4 respectively. In Experiment 1, the t-tests revealed that, in the group for which the fixation distance was far, all PSS values from trials with an unilateral cue were different from 0 (all $t(10) > 3.90$, all $p < .004$). In the group for which the fixation distance was near, the PSS values for unilateral cue trials were significantly different from 0 (all $t(9) > 2.80$, all $p < 0.04$), but not when the visual cue was in far space, and participants had to indicate which hand was stimulated first ($t(9) = 1.81$; $p = .10$). By contrast, none of the PSS values from trials with bilateral cues were significantly different from 0 ms, nor for the trials where the fixation distance was far (all $t(10) < 1.5$, $p > 0.15$), nor for the trials where the fixation distance was near (all $t(9) < 1.7$, all $p > .13$). This result indicates that the PSS is only biased by the presence of an unilateral visual cue, and never by the presence of bilateral cues. In addition, these results suggests that the bias is always significant in the presence of a unilateral visual cue in near space, while it could depend on the position of the fixation point if a bias is present for the unilateral visual cues in far space.

The ANOVA revealed a significant main effect of *visual cue type* ($F(1,19) = 28.05$, $p < .001$, $d = 1.76$) suggesting that PSS values were larger for unilateral than bilateral cues conditions. The ANOVA also revealed a main effect of *cue distance* ($F(1,19) = 7.66$, $p = .01$, $d = 0.57$), suggesting that PSS values were larger when the cues were presented in near space than when they were presented in far space. However, the significant interaction between *visual cue type* and *cue distance* ($F(1,19) = 7.97$, $p = .01$, $d = 0.51$) suggests that the effect of the distance of the cue on the PSS depended on the type of cue presented. Indeed, the spatial location of the cue had a significant impact in trials with an unilateral cue ($F(1,19) = 14.69$, $p = .001$, $d = 0.68$), but not in trials with a bilateral cue ($F(1,19) = 0.046$, $p = .83$) (Figure 4). In addition to the results of the t-tests, this suggest that a unilaterally presented visual cue, gave rise to an attentional bias to the side of the cue, and, more crucially, this bias was more pronounced

when the visual cue occurred in near space than when it occurred in far space. The factors of *task* and *fixation distance* had no effect on participants' performance, except for a significant interaction between *task*, *cue distance*, and *fixation distance* ($F(1,19) = 7.42$; $p = .01$, $d = 1.17$), and a significant interaction between *visual cue type*, *task*, *cue distance*, and *fixation distance* ($F(1,19) = 8.40$, $p = .009$, $d = 1.28$). The 4-way interaction can be attributed to the fact that, while the PSS values in the unilateral cue condition were not dependent on the task nor on the fixation distance (*task*cue distance*fixation distance* interaction: $F(1,19) = 0.28$; $p = .60$), these latter factors influenced the PSS in the bilateral cue condition (*task*cue distance*fixation distance* interaction: $F(1,19) = 12.74$, $p = .002$, $d = 1.56$). This result was not further investigated because previous analyses showed that none of the PSS values for the bilateral cue conditions were significantly different from 0 ms, and the interaction included procedural variables that were of no further theoretical interest. None of the other comparisons were significant (all $F(1,19) < 1.30$, $p > .25$).

The results of Experiment 2 were similar (see Figures 3 and 4). First, the t-tests revealed the presence of a bias significantly affecting the PSS in all trial types having an unilateral cue (all $t > 3.33$, all $p < .007$), whereas such a bias was not significantly different from 0 ms in those trials with bilateral cues (all $t < 1.26$, all $p > .23$). The repeated measures ANOVA revealed a significant main effect of *visual cue type* ($F(1,11) = 14.08$, $p = .003$, $d = 1.78$), a main effect of *cue distance* ($F(1,11) = 10.04$, $p = .009$, $d = 0.82$), and a significant interaction between these factors ($F(1,11) = 12.74$, $p = .004$, $d = 0.93$). This result confirmed that the bias was more pronounced when unilateral cues were presented in near space than when they were presented in far space (main effect of *cue distance* in those trials with an unilateral cue: $F(1,11) = 14.80$, $p = .003$, $d = 0.80$). In those trials with bilateral cues, there was no difference between cues in near vs. far space ($F(1,11) = 2.49$, $p = .14$).

JND. The mean JND data are shown in Figure 4. The only noticeable result was a main effect of *cue distance* which reached significance in Experiment 2 ($F(1,11) = 7.05, p = .02, d = -0.54$), but which was not significant in Experiment 1 ($F(1,19) = 3.11, p = .09$). This result suggests that participants found it more difficult to identify which of the IES was first/last when visual cues were presented in near space as opposed to when cues were presented in far space. None of the other effects were significant (all $F < 3.70, p > .08$).

4. Discussion

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

An intriguing question concerns how people localize nociceptive stimuli on their body. Humans have the ability to localize cutaneous pain almost flawlessly (Koltzenburg, Handwerker, & Torebjörk, 1993; Mancini et al., 2011a; Moore & Schady, 1995; Trojan et al., 2006). However, a physical threat is rarely unisensory, and a purely anatomical frame of reference might be insufficient to localize which of the objects in external space is damaging

the body (Moseley, Gallace, & Spence, 2012). Indeed, the ability to localize somatosensory stimuli not only relies on the adequate representation of the space of the body, but also on the ability to represent external space with respect to that body. Non-somatotopic frames of reference are, then, necessary to rapidly attend to, or direct actions toward, objects that could have a potential impact on the body. In the context of pain, this was illustrated by Moseley et al. (2009) in CRPS patients. Using a TOJ task with two concurrent tactile stimuli being applied sequentially, one to either hand, these authors showed that, in CRPS patients, the perception of the stimuli applied to the affected hand tends to be extinguished when the hands are in normal posture. However, when the patient's hands were crossed over the sagittal midline of the body, the reverse pattern was observed: The perception of the stimuli applied to the unaffected hand tended to be extinguished (Moseley et al., 2009). This result suggests that the deficits in spatial perception observed in CRPS patients are not related to the pathological limb but rather to the space normally inhabited by the pathological limb. In other words, neglect-like symptoms induced by unilateral pain, such as in the case of CRPS, revealed the existence of a *spatiotopic* reference frame (Smania & Aglioti, 1995), integrating the processing of both somatosensory and proprioceptive information. Even more striking, the same authors have shown that the skin temperature on the hands was not only dependent of their relative position in external space (Moseley, 2012) but also on the visual perception of their position (Moseley, Gallace, Di Pietro, Spence, & Iannetti, 2013). Indeed, they demonstrated that when the pathological hand was viewed through prism glasses to appear on the healthy side of the body, the temperature of that hand warmed up. This latter study illustrates a potential role of vision in the deficits observed in CRPS. Similar crossmodal effects between nociceptive processing, proprioception and vision were also observed in healthy volunteers (Lloyd, Morrison, & Roberts, 2006; Longo, Betti, Aglioti, & Haggard, 2009; Mancini, Longo, Kammers, & Haggard, 2011; Martini, Valentini, & Aglioti, 2013;

Sambo et al., 2012a, 2012b, Sambo & Iannetti, 2013). Other studies support the idea that such integration is made according a spatiotopic representation of the space of the body (Gallace et al., 2011; Sambo et al., 2013).

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

The existence of a peripersonal frame of reference has already been demonstrated for the mapping of tactile stimuli and supposedly relies on the existence, at least in monkeys, of bimodal neurons mostly in the ventral premotor cortex and the ventral intra-parietal sulcus (Graziano & Gross, 1994). For example, Graziano and Gross (1998) demonstrated that neurons in the ventral premotor cortex of monkeys fire both for tactile and visual stimuli, and that their visual receptive fields (RF) extends from the approximate region of the tactile RF

into the immediate adjacent space. Similarly, Dong et al. (1994) found in area 7b, in the inferior parietal lobe of monkeys, neurons that respond to nociceptive stimuli and to dynamic visual stimuli moving towards the RF of these neurons and static visual stimuli presented in the vicinity of the somatosensory RF. Dong et al. (1994, pp. 561) suggested that this area would provide “(...) *dynamic visual-somatic information about an approaching noxious stimulus and impending tissue damage, respectively, may be necessary for directing motor adjustments (...) to minimize body exposure and contact with the offending stimulus*”.

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

Based on the present results, it is reasonable to hypothesize that premotor and parietal areas play an important role in nociceptive processing and pain perception both in healthy individuals (Legrain, Iannetti, Plaghki, & Mouraux, 2011) and in chronic pain patients (Maihofner et al., 2007). Indeed, nociceptive inputs that are perceived as painful activate a large array of cortical areas such as mainly operculo-insular and cingulated areas, but also frontal and parietal areas (Tracey & Mantyh, 2007). Recently, the common view according to

which some of these areas could be specifically involved in nociceptive processing and pain perception was challenged. Some authors have argued that such activity instead reflects the detection, localization, and reaction to sensory events that are meaningful for the integrity of the body (Legrain et al., 2011). As such, areas like frontal and parietal areas may be involved in the integration of nociceptive information into a multisensory representation of the body and the space nearby. By using peripersonal frames of references to code the spatial location of nociceptive stimuli, the brain can form an integrated representation of the part of the body in pain and the location of the external object causing that pain. Nociceptive inputs are integrated into a multisensory system that monitors the space of the body and the region of external space immediately surrounding the body, detects any sensory information having a potential impact on the body, and informs the individuals about changes in the representations of the body. The ultimate aim of the system would be to facilitate the processing of physical threat and to select and prepare the most appropriate response (Graziano & Cooke, 2006). Therefore, the coding of nociceptive information in a peripersonal frame of reference may constitute a safety margin around the body that is designed to protect it from potential physical threat and represents a mechanism for preserving homeostatic control over the body (Moseley et al., 2012).

Furthermore, the present findings point at the potential relevance of spatial perception to the understanding of the pathophysiology and the treatment of chronic pain. For example, an etiology close to hemispatial neglect was described in CRPS patients (see Legrain, Bultitude, De Paepe, & Rossetti, 2012). As already explained, a phenomenon similar to tactile extinction is observed in these patients when a TOJ task is used (Moseley et al., 2009). Intriguingly, this pattern of sensory deficits tends to be reversed by changing the posture. Similarly, displacing the position of the CRPS hand either *proprioceptively* (by crossing the hands; Moseley, Gallace, & Iannetti, 2012) or visually (by prism glasses; Moseley et al., in press) also

modifies the skin temperature of the CRPS hand. This illustrates that sensory and vegetative symptoms in chronic pain may be determined by higher-order cognitive processes involved in the representation of the body (Moseley et al., 2012). Sumitani et al. (2007) showed a displacement of the body midline estimation towards the affected side of the body in CRPS patients (however see Kolb, Lang, Seifert, & Maihofner, 2012; Reinersmann et al., 2012). Using prismatic visuomotor adaptation, these authors succeeded to reduce the displacement of the body representation. Importantly, they also showed that prismatic adaptation can alleviate pain and reduce associated CRPS symptoms such as edema, discoloration and motor impairment. Bultitude and Rafal (2010) reproduced these results in one patient showing that the benefits of the procedure were dependent of the use of the pathological hand during the prism adaptation. These latter studies illustrate the importance of understanding the mechanisms underlying the integration of nociceptive information in the multisensory representation of the bodily space for the rehabilitation of chronic pain patients.

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

555 The present study has a number of limitations that the reader should be made aware of. First,
556 further studies are needed in order to determine whether crossmodal shifts in the PSS between
557 vision and nociception reflect exogenous shifts of spatial attention from one space (i.e.,
558 external proximal space) to another space (i.e., bodily space) or intrinsic multisensory
559 integration (Spence, McDonald, & Driver, 2004b). Second, although the participant's head
560 was fixed to minimize head movements and to prevent vision of the hands, we cannot
561 completely rule out the possibility that spatial attention was overtly shifted towards the
562 location of the unilateral cues, and therefore to the hand positioned close to the cue, if cues
563 were presented in near space. In this case, an alternative interpretation of our results would be
564 that the selective vision of one of the hands primed the processing of nociceptive stimuli
565 applied to that hand. However, this interpretation seems unlikely. Given that the distances
566 between the hands and the trunk and the chin-rest and the trunk were respectively 40 cm and
567 10 cm, rapid gaze shifts from fixation point towards the hands seem highly unlikely.
568 Furthermore, it is commonly acknowledged that fast eye movements such as saccades take at
569 least 200 ms to initiate and 20-200 ms to reach the target (depending on its eccentricity)
570 (Kandel, Schwartz, & Jessell, 2000), a total duration largely superior to the delay between the
571 visual cue and the second nociceptive stimulus, even in the conditions with the largest SOAs.
572 Third, replications are also needed in order to circumvent the loss of participants due to their
573 inability to perform the task at the required level. This could be attributable (1) to the low
574 intensity of the nociceptive stimuli, which was needed to guarantee the selectivity for
575 nociceptor activation (Mouraux et al., 2010), and (2) to jitter in input transmission due to the
576 variability of the conduction velocity of A δ fibers (Adriaensen Gybels, Handwerker, & Van
577 Hees, 1983). Indeed, according to the Erlanger-Gasser classification of sensory fibers, the
578 conduction velocity of A δ fibers goes from 3 to 30 m/s. This variability in peripheral
579 transmission might have made the temporal judgments more difficult, especially for trials

with short SOAs. Nevertheless, it is worth noting that this loss did not prevent the observation of significant crossmodal shifts of the temporal order judgment of nociceptive stimuli.

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Conflict of interest statement

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

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800

801 **Figure 1.** Illustration of the experimental set-up for Experiment 1 (A and B) and Experiment
 802 2 (C). Nociceptive stimuli, represented by the red lightning symbols, were applied to both of
 803 the participant's hands. Visual cue stimuli, represented by the green circles, were presented at
 804 four different locations in each trial: either unilaterally or bilaterally, and either on the

participant's hands (in near space) or in front of the participant's hands (in far space). In Experiment 1, half of the participants fixated on a computer screen that was located 100 cm in front of their trunk (A), for the other half of the participants the screen was located 40 cm in front of their trunk (B). In Experiment 2, the participants fixated on a red LED that was situated equidistant between the near and far visual cues (C).

Figure 2. Time-course of one trial in Experiment 1. In Experiment 2, the time-course was identical, but the computer screen was replaced by a red LED. This fixation LED stayed on during the entire trial, and was turned off after the participant had made a response.

816

817 **Figure 3.** Nociceptive temporal order judgments (TOJs) in Experiments 1 and 2. The figure
 818 illustrates the fitted curves from the cumulative data of the 19 and 12 participants who
 819 successfully completed Experiments 1 and 2, respectively. The data from the two subgroups
 820 of participants having participated in Experiment 1 (fixation far vs. close) and the data from
 821 the two tasks in each experiment (‘Which stimulus first?’ vs. ‘Which stimulus second?’) are
 822 merged. The graphs in the upper part of the figure represent the performance on those trials
 823 during which a single visual stimulus was presented unilaterally. The X-axis represents the
 824 different SOAs between the two nociceptive stimuli presented in a trial. As the aim of the

study was to evaluate the crossmodal effect of unilateral visual cues on the TOJ for nociceptive stimuli, the responses were recoded so that negative values on the left side of the X-axis indicate that the cued hand was stimulated first, while positive values indicate that the uncued hand was stimulated first. The Y-axis represents the mean proportion of responses according to which the cued hand was perceived as having been stimulated first. The graphs in the lower part of the figure represent the performance on those trials where two visual stimuli were presented bilaterally. As, in this case, both sides were always cued simultaneously, the distinction between left hand and right hand was maintained: negative values on the left side of the X-axis indicate that the participant's left hand was stimulated first, while positive values that the right hand was stimulated first. The Y-axis represents the mean proportion of responses according to which the left hand was perceived as being stimulated first. Solid blue lines illustrate the fitted curves to the trials during which the visual stimuli were presented in near space, the broken red lines the fitted curves to the trials during which the visual stimuli were presented in far space. As compared to the bilateral cue conditions, the curves in the unilateral cue conditions were shifted toward the uncued side, indicating that the nociceptive stimulus presented on the uncued side had to be presented several milliseconds before the cued stimulus in order to have an equal chance as the stimulus at the cued side of being perceived first. The PSS values that differed significantly from 0 ms are depicted in the figures with arrows. The JND can be inspected by looking at the slope of the curves. A steep slope indicates that participants' judgments were consistently right, while a flatter slope indicates that the participants found the task harder to perform, and consequently, made more mistakes. As the JND corresponds to $0.675/\text{slope}$, the steeper the slope, the smaller the JND.

Figure 4. Means and standard deviations for the point of subjective simultaneity (PSS) and the just noticeable difference (JND) in Experiments 1 and 2. The PSS and JND scores were calculated for each participant and each condition separately. The data from the two groups of participants having participated to Experiment 1 (fixation far vs. close) and the data from the two tasks in each experiment (“Which stimulus first?” vs. “Which stimulus second?”) are merged. In both experiments, PSS values were significantly different from 0 ms during trials with unilateral visual cues, but not during the trials with bilateral cues. In the former condition, the PSS was larger when the unilateral cue was presented in near space as compared to when it was presented in far space. The JND values were significantly larger

859 when the visual cues were presented in near space than when they were presented in far space
860 (in Experiment 2 only). Error bars represent standard errors corrected according the method of
861 Cousineau (2005).