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Research article

Investigating peri-limb interaction between nociception and vision using spatial depth

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HIGHLIGHTS

- Nociception influences the perception of visual stimuli around the body.
- Such a crossmodal influence relies on multisensory representations of body parts.
- Global representation of the body as a whole is less important in such interactions.
- The data are clinically relevant to understand cognitive biases in chronic pain.

ABSTRACT

In order to adapt behavior to a potentially body damaging threat, it is crucial to coordinate the perception of the location of the threat in external space and that of the location of the potential damage on the body surface. Such ability presupposes interactions between nociceptive stimuli and visual stimuli occurring close to the body. We hypothesized that these interactions would rely on multisensory representations of each limb itself, extending its boundaries slightly into external space, with less influence of the global representation of the body as a whole. In most studies investigating such representations, spatial organization of the somatic and extra-somatic stimuli is made according to an egocentric frame of reference centered on the main axes of the participant's whole body (e.g. the trunk), dissociating the left vs. the right side of space. Here, the contribution of such a body-centered frame was minimized, by placing participants' hands in front of them along their anteroposterior body axis, one at a proximal, the other at a distal location. They performed a temporal order judgment task on pairs of visual stimuli, one delivered close to each hand. Visual stimuli were preceded by nociceptive stimuli applied either on one hand, or on both hands simultaneously (control condition).

Results showed that, as compared to the control condition, participants' judgements were biased in favor of the visual stimuli the closest to the stimulated hand, irrespective of their distance from the trunk. This finding supports the idea that the mechanisms underlying nociceptive-visual interactions are based on spatial representations that primarily use the stimulated limb rather than the whole body as a coordinate system.

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1. Introduction

Monitoring the space of the body and the external space around the body is of primary importance to identify and react to stimuli that might inflict physical damage on the body. Such ability is thought to rely on the existence of specific representations of the body, namely peripersonal representations, slightly extending their physical boundaries into external space in order to integrate somatic and non-somatic (e.g. visual) stimuli [1]. Such multisensory peripersonal representations have been largely evidenced for the spatial perception of touch [2], and have also recently been shown to be involved in the processing of nociceptive stimuli [3–5], that is, stimuli activating the neurophysiological system involved in transmitting inputs about potentially harmful sensory events to the cortical brain. Most of these studies used temporal order judgment (TOJ) tasks during which participants discriminate the

temporal order of two stimuli presented in rapid temporal succession. These tasks are classically used to measure effects of selective attention, and are grounded on the theory of prior-entry according to which the processing of attended stimuli is speeded-up as compared to unattended ones [6]. In these studies [3–5], pairs of nociceptive stimuli were presented to the participants, one on each hand, and they judged which of the two hands they perceived as having been stimulated first. Slightly before the nociceptive stimuli, a visual stimulus was presented in either the left or the right side of space, at different locations relative to the hands. It was shown that the participants' judgments were biased to the advantage of the perception of the nociceptive stimuli applied on the hand the closest to the visual stimulus, irrespective of the relative position of the hands and the visual stimuli in external space [5]. These studies thus suggest that the perception of nociceptive stimuli depends on the vision of an object occurring in external space that might have an immediate impact on the body. However, investigating the reverse link, that is, how the perception of visual space can be influenced by bodily sensations, seems also ecologically, and, most notably, clinically relevant. Indeed, it has been recently shown that patients with unilateral chronic pain can be characterized by difficulties in representing and perceiving the affected limb [7], and, in addition, in perceiving visual stimuli presented in the side of space ipsilateral to the affected limb [8]. The aim of the present study was therefore to understand how a nociceptive stimulus applied to a specific limb could impact the perception of a visual stimulus occurring in the peripersonal space of that stimulated limb. The second aim was to disentangle whether nociceptive-visual interactions are mostly facilitated by a peripersonal representation of space centered on the stimulated limb itself, that is, a body representation extending in the close vicinity of the limb, or a global peripersonal representation of the body as a whole, according to which objects can be reached by upper-limb movements. In previous studies [3–5], nociceptive-visual interactions were actually investigated using the main spatial organization of the body, dissociating the left and the right sides of space, which are always defined according to a global egocentric frame of reference, that is, the midsagittal plane of the participant's whole body [1]. Indeed, although in these studies the largest significant effect was always observed for visual stimuli the most proximal to the hands, the results showed that nociceptive stimuli were in each case influenced by visual stimuli presented ipsilaterally to the stimulated hemibody, even those presented more distally from the hands. Here, in order to minimize confusing effects of a possible whole-body representation, and to investigate the specific contribution of a peri-limb representation to nociceptive-visual interactions, we avoided the classic left-right dimension usually used in TOJ tasks. Indeed, visual stimuli and the stimulated hands were not aligned anymore according to the left vs. right side of space, but along the midsagittal plane of the body. Therefore, the perception of visual space was not manipulated anymore according to the left vs. right side of space, but according to the depth along the anteroposterior axis of the body. Similarly, although nociceptive stimuli were still applied to the two opposite hemibodies, the left and right hands were placed *proximally* vs. *distally* from the participants' trunk. Concretely, participants were asked to perform a TOJ task on pairs of visual stimuli, one occurring close to (i.e. at a proximal location), the other one far from (i.e. at a distal location) the participants' trunk while one hand was placed close to each visual stimulus. Nociceptive stimuli were applied on one of the two hands. We hypothesized that participants would prioritize the perception of the visual stimuli occurring close to the stimulated hand, regardless of which hand was stimulated and of the distance of the visual stimuli from the trunk.

2. Methods

2.1. Participants

Sixteen paid participants took part in the experiment (mean age: 21.87 ± 3.42 years, range: 18–32 years, 13 women). The sample size was chosen based on previous studies that succeeded to observe significant effects with similar designs and equivalent sample size (e.g. [3–5]). Participants had no prior history of neurological, psychiatric, heart and chronic pain disorders, no trauma of the upper limbs in the previous six months and no regular drug intake, including painkillers and anti-inflammatory within the 12 h before the experiment. All of them had normal to corrected-to-normal vision and slept at least 6 h the night preceding the experiment. According to the Flinders Handedness Survey [9], 14 participants were right-handed. Written informed consents were obtained and all experimental procedures were approved by the local ethics committee in agreement with the latest version of the Declaration of Helsinki.

2.2. Stimuli and apparatus

Visual stimuli were presented by means of two light-emitting diodes (LEDs), a red one (625 nm wavelength at 20 mA, 756 mcd luminous intensity, 120° viewing angle) and a blue one (465 nm wavelength at 20 mA, 370 mcd luminous intensity, 120° viewing angle) (Multicomp, Farnell element14, Leeds, UK). A third yellow LED (591 nm wavelength, 700 mcd luminous intensity at 20 mA, 120° viewing angle) was used as fixation point during the task. During the experiment, the red and blue LEDs were illuminated with a 5 ms duration and were perceived by the participants as brief flashes. Their colors were clearly discriminated by all participants. One of the two experimental LEDs was placed ~32 cm from the edge of a table in front of the participant (proximal location), the other one at a distance of ~60 cm (distal location), both on a straight line perpendicular to the table's edge. The order in which red and blue LEDs were placed either at the proximal or the distal location was counterbalanced across participants. The yellow fixation LED was placed equidistantly from the red and blue LEDs on the same line.

Nociceptive stimuli were applied on the hands' dorsa by means of intra-epidermal electrical stimulations (IES) using stainless steel concentric bipolar needle electrodes (Nihon Kohden, Tokyo, Japan) [10]. The needle cathode was of 0.1 mm in length and 0.2 mm in diameter and was surrounded by a cylindrical anode of 1.4 mm in diameter. By gently pressing the electrode against the skin, the needle cathode was inserted into the epidermis in the sensory territory of the superficial branch of the radial nerve. The absolute detection threshold of the IES to a single 0.5 ms square-wave pulse was established for each hand separately using a staircase procedure [11]. Once determined, the threshold values were doubled. Using IES based on such a procedure has been shown to specifically and selectively activate skin Aδ nociceptors [12]. IES intensities were adjusted if necessary so that they were perceived as equally intense between the two hands, but with values no more than 0.5 mA [13]. Adjustments were made to avoid unbalanced intensities between the cue conditions (i.e., proximal vs. distal cueing, see Procedure). During the experiment, nociceptive stimuli consisted of trains of 3 consecutive 0.5 ms IES pulses separated by an interpulse interval of 5 ms. Sensations were described by the participants as pricking. After each block of stimulation, participants were asked to rate verbally the perceived intensity of the nociceptive stimuli on a scale ranging from 0 (=not perceived) to 10 (=very intense), in order to ensure that (1) there was no habituation and the stimuli were still perceived as pricking, and (2) their intensities were qualified as equivalent between the two hands. If necessary, stimulus intensi-
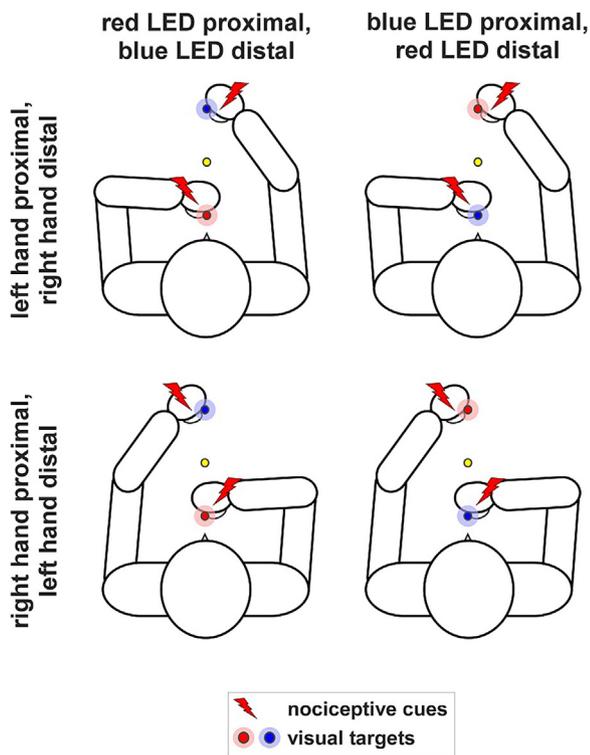
red LED proximal, blue LED distal   **blue LED proximal, red LED distal**

nociceptive cues
visual targets

Fig. 1. Illustration of the experimental set-up. Participants performed a temporal order judgment task on two colored LEDs (i.e. red and blue), placed equidistant from a yellow fixation LED along the participants' anterioposterior body axis. Participants placed each hand close to one of the target LEDs, so that both the hands and the targets LEDs were positioned at a proximal vs. distal location. Slightly before the presentation of visual stimuli, nociceptive stimuli (represented by red flashes) were applied either on both hands simultaneously or on one single hand. The positions of the colored target LEDs and of the hands were counterbalanced across participants. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ties were adjusted in order to meet both criteria, with 0.5 mA as a limit. If none of the criteria was met and the limit reached, the electrodes were displaced and the threshold measurement restarted before starting the next block [13]. For analyses, stimulus intensities were characterized for each hand by the highest intensities of current adjusted during the experiment.

2.3. Procedure

The participants were sitting on a chair placed in front of a table in a dimly illuminated testing room. Their arms rested on the table and their head was placed in an individually adapted chin-rest to avoid head movements. Participants sat in a way that the three LEDs were positioned along their body's midsagittal plane, in front of them. After the threshold measurements, the participants were asked to place their hands on the table, palms down, one close to each of the target LEDs, so that the LEDs were placed between the thumb and the index finger of each hand. Hence, one of the hands was positioned proximally to the body trunk, whereas the other one was placed distally to it, according to the anteroposterior axis (i.e. in line with the body sagittal plane). The position of the hands were counterbalanced across participants, with half of the participants placing their left hand at the proximal location and the right hand at the distal location, and the other half of participants doing the reverse (see Fig. 1).

The participants were presented with one practice block of 10 trials, with only the two largest time intervals (i.e. SOAs, stimulus onset asynchronies, see below) between the two visual stimuli, and two experimental blocks of 90 trials each. One experimental

block lasted about 8 min. A trial started with the illumination of the yellow fixation LED, which remained illuminated during the whole trial. The participants were asked to maintain their gaze on that LED. Five hundred ms after the fixation light onset, a nociceptive stimulus was applied either on one of the hands (*single cueing condition*) or on both hands at the same time (*simultaneous cueing condition*). In the single cueing conditions, the nociceptive stimulus was applied either on the hand the closest to the trunk (i.e. the hand next to the proximal visual stimuli) or on the hand the furthest from the trunk (i.e. the hand next to the distal visual stimuli). The three conditions, *single proximal cueing, single distal cueing* and *simultaneous cueing,* were equiprobably and randomly presented across trials. After 200 ms, the pair of visual stimuli was presented, one stimulus flashed close to each hand. The two visual stimuli were separated in time by twenty possible stimulus onset asynchronies (SOAs): $\pm 200, \pm 145, \pm 90, \pm 75, \pm 60, \pm 45, \pm 30, \pm 15, \pm 10, \pm 5$ ms. Negative values indicate that the proximal visual stimulus was presented first, while positive values indicate that the distal visual stimulus was presented first. The presented SOAs were determined according to the adaptive PSI method, and selected trial by trial considering the performance of the participant in all the previous trials within one cueing condition [14,15]. This method mainly aims to estimate the parameters of interest without probing extensively all the SOAs. The participants were instructed to not respond to the nociceptive stimuli but to verbally report the color of the visual stimulus that was perceived as being presented first in one block and the color of the one that was perceived as being presented second in the other block. These two different response conditions were used to prevent that any potential response bias could be mistaken for a perceptual spatial bias [6]. The order of the two blocks was counterbalanced across participants. The participants' responses were encoded by the experimenter by pressing a key that switched off the fixation LED and triggered the next trial 2000 ms later. Participants were instructed to be as accurate as possible and that speed was not relevant for the task. The participants were not given any feedback regarding the accuracy of their responses. The whole experiment took on average 30–45 min.

2.4. Measures

Data were fitted online during the experiment with a logistic function from which the parameters of interest (α, the threshold, and β, the slope) were derived. The parameter estimates correspond to the values of the last update computed by the adaptive algorithm [14,15]. The first parameter is the α of the logistic function, which corresponds to the point of subjective simultaneity (PSS) and refers to the SOA at which participants report the two events (i.e. the illumination of the proximal and the distal LEDs) as occurring first equally often (i.e. the 0.5 criterion on the ordinate). The PSS is thus the amount of time by which one stimulus has to precede or follow the other one in order to be perceived as occurring simultaneously [16]. The slope of the function, i.e. the β, describes the noisiness of the participant's performance, and corresponds to the precision of the participant's responses during the experiment [15]. For all cueing conditions, the proportion of proximal visual stimuli having been reported as perceived first was plotted as a function of SOA.

2.5. Analyses

Variables referring to the hands' and LEDs' positions were coded according to the distance from the trunk (i.e. proximal vs. distal). In order to test the presence of biases in the participants' judgments, PSS values were compared to 0 by using *t*-tests. Next, to compare the different experimental conditions, a repeated-measures anal-

ysis of variance (ANOVA) was performed on PSS and slope values with *cueing condition* (*single proximal* vs. *single distal* vs. *simultaneous*) as within-subject factor. Greenhouse-Geisser corrections and contrast analyses were used if necessary. Significance level was set at p ≤ 0.05.

3. Results

3.1. Intensity of the nociceptive stimuli

The mean values of the maximal intensity of the nociceptive stimuli applied on the proximal hand and the distal hand were 0.30 ± 0.9 mA and 0.25 ± 0.08 mA respectively, and were significantly different ($t(15)= 2.66$, $p=0.018$). These values are in the range of those used in previous studies to activate selectively skin nociceptors without concomitant activation of mechanoreceptors [12,13]. The self-reported intensities were on average 4.94 ± 1.78 and 5 ± 1.81 for proximal and distal hands respectively, and were not significantly different ($Z=-0.82$, $p=0.414$).

3.2. PSS and slope

The fitted psychometric curves of the TOJ performances averaged across participants per condition are shown in Fig. 2A. The *t*-tests revealed that the PSS values from the *single proximal* ($M=23.00 \pm 23.85$) and *simultaneous* ($M=9.58 \pm 13.04$) cueing conditions were significantly larger than 0 ($t(15)=4.03$, $p= 0.001$, $t(15)=2.94$, $p=0.010$, respectively), while the PSS value for the *single distal cueing* condition ($M=-12.76 \pm 19.65$) was significantly smaller than 0 ($t(15)=-2.60$, $p= 0.020$). This indicates that judgments were biased in all three conditions, towards the visual stimuli presented close to the hand at a proximal location for the *single proximal* and *simultaneous* cueing conditions, and towards the visual stimuli presented close to the hand at a distal location in the *single distal* cueing condition. The ANOVA performed on the PSS values revealed a significant main effect of the factor *cueing condition* ($F(2,14)=15.59$, $p=0.001$, $\eta^2 p=0.56$). Contrasts analyses showed that the PSS in the *single proximal* cueing condition was significantly larger ($t(15)=2.84$, $p=0.013$), while the PSS in the *single distal* cueing condition was significantly smaller ($t(15)=-4.15$, $p=0.001$) as compared to the PSS in the *simultaneous* cueing condition (Fig. 2B). In addition, in order to compare the PSS values of the *single distal* and *proximal* cueing conditions, the PSS values of the *simultaneous* cueing condition were subtracted from the PSS values of each single cueing condition respectively (i.e. proximal vs. distal) for each participant. This was intended to use the PSS value of the *simultaneous* cueing condition as a baseline, instead of 0, since the PSS value of that condition was used as a neutral condition [18] and was significantly different from 0. The difference between absolute values of the mean deltas was not significant ($t(15)=-1.44$, $p=0.169$), suggesting effects of similar size for both *single distal* and *single proximal* cueing conditions. Finally, the ANOVA performed on the slope values did not reveal any significant effect of the factor *cueing condition* ($F(2,14)=0.16$, $p=0.852$).

4. Discussion

This study aimed to investigate the ability to represent a spatial extension of the body space in order to prioritize the processing of external stimuli that might have an impending impact on the body's integrity. More specifically, we demonstrated that a nociceptive stimulus inflicted onto one hand impacts the perception of visual stimuli presented in the vicinity of the stimulated hand. The participants performed a TOJ task on two visual stimuli placed along the anteroposterior axis in front of them, at two different

distances from the body, proximally vs. distally from it. One hand was placed next to each visual stimulus. This specific experimental setting allows investigating the effect of the peripersonal representation of the limb, i.e. the peri-limb representation, on crossmodal interaction between somatic and non-somatic stimuli, while minimizing the effect of the classic spatial dissociation into left vs. right side of space. Opposing left and right sides of space often involves an egocentric frame of reference, which is defined by the main axes of the body such as the midsagittal plane, mainly represented by the body trunk. Therefore, by placing the hands and the visual stimuli along the anteroposterior axis in front of the participants, we limited the contribution of the anatomical representation of the body as a whole. Indeed, although nociceptive stimuli were still applied on the left vs. right hand according to an anatomical reference frame, the position of the hands and the visual stimuli in external space, as well as the spatial congruence between the locations of the stimuli from both modalities, were completely independent of the classic lateral spatial organization, and rather defined in terms of spatial depth (i.e. proximal vs. distal). In addition, participants' responses in the task were given according to the color of the visual stimuli, and not their location, so that space was irrelevant for the response mode, avoiding any confounding effects of non-orthogonal response modalities [6]. In a first condition, which served as a control condition, nociceptive stimuli were applied on both hands simultaneously, a few milliseconds before the visual targets. Attentional prioritization in TOJ tasks is usually highlighted by shifts in the PSS [6]. We observed that PSS values in this control condition were shifted towards the visual stimulus at a distal location. Visual stimuli presented distally had thus to be presented about 10 ms before the ones presented proximally in order to be perceived as being stimulated first equally often. In other words, judgments were biased to the advantage of the proximal visual stimuli, suggesting that the perception of visual stimuli occurring close to the body received more attentional weight than those presented far from it. It seems unlikely that this could be accounted for by the difference in terms of the intensity of the electrical current between the two IES cues, since this physical difference was marginal and not reflected by a difference in terms of subjective perception. The proximal priority would be rather in favor of a default use of a whole-body peripersonal representation. In addition, it supports the idea that we prioritize the processing of sensory events occurring close to our body because they might have a greater behavioral relevance due to their potential impending impact on the body. Many studies support the dissociation between the peripersonal frame of reference, coding the near space close to the body, and the extrapersonal frame of reference, coding the far out-of-reach space, which probably rely on different cortical networks [1]. Paying more attention to sensory events arising near the body would optimize contacts and manipulation of innocuous objects, but also defensive behaviors against noxious objects in order to protect the physical integrity of the body [19]. However, the priority for proximal visual stimuli after simultaneous nociceptive stimulation could also be explained in terms of a difference between lower and upper visual hemifields. Indeed, our participants were asked to fixate their gaze right in the middle between the proximal and the distal visual stimuli, so that the proximal visual stimuli were presented in the lower hemifield, and distal visual stimuli in the upper hemifield. Experiments have demonstrated the dominance of the lower visual field in several aspects of visual perception, such as contrast sensitivity, visual acuity and spatial resolution [20,21]. Nevertheless, the most striking result of the present study is that, as compared to the simultaneous cueing condition, in the single cueing conditions, the direction of the PSS and, consequently, of the perceptual bias, depended on the hand on which the nociceptive stimulus was applied (i.e. the one in proximal vs. distal location), independently of the stimulated hand according
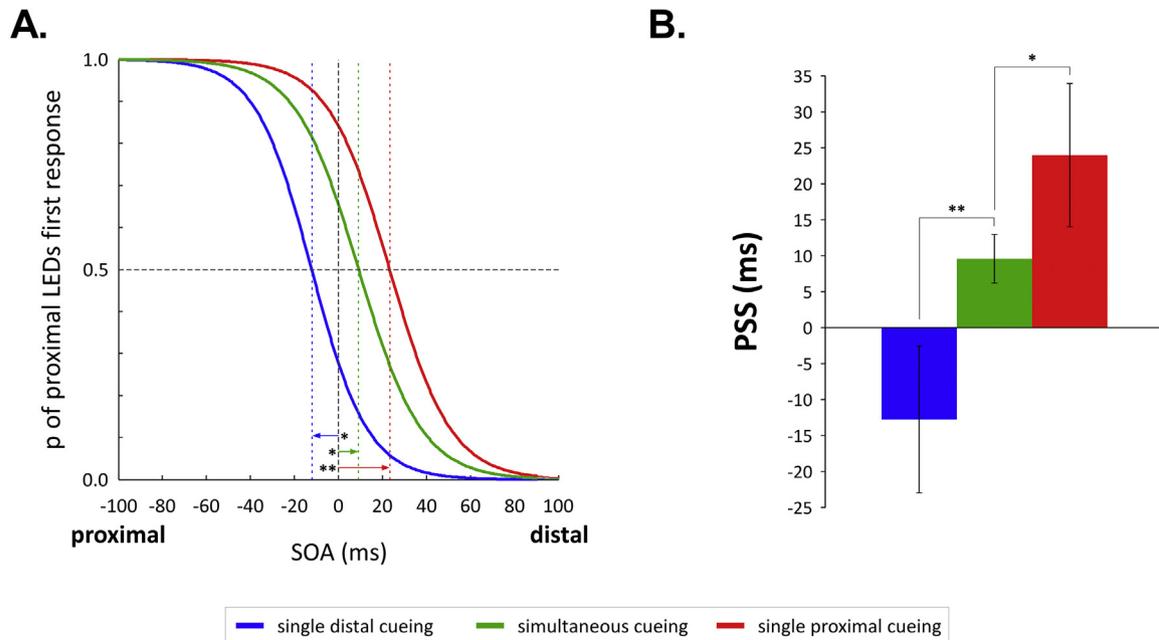
Fig. 2. Visual temporal order judgements (TOJs). (A) Fitted curves of the psychometric function from the data of the 16 participants according to the cueing conditions. The x-axis represents different possible SOAs. Negative values indicate that the proximal visual stimulus was presented first, and positive values that the distal visual stimulus was presented first. The y-axis represents the proportion of trials in which the proximal visual stimulus was perceived as occurring first. The sigmoid curves fit respectively the data of the single distal cueing condition (blue), the simultaneous cueing condition (green), and the single proximal cueing condition (red). The respective points of subjective simultaneity (PSS) were obtained by deriving the x-values of the points of the fitted curves with (x, 0.5) as coordinate. (B) Mean values of the PSS for the single proximal cueing condition (red), the simultaneous cueing condition (green) and the single distal cueing condition (blue). Error bars represent the 95% confidence intervals adapted according to Cousineau's method [17]. $^{*} = p \leq 0.05$, $^{**} = p \leq 0.001$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

to the anatomical reference (i.e. the left or right hand). When a nociceptive stimulus was applied on the hand proximal from the body trunk, PSS values were shifted towards the distal visual stimuli, and were significantly larger than the ones obtained in the simultaneous cueing condition, although the direction of the bias was the same. Conversely, when the nociceptive stimulus was applied on the hand distal from the trunk, PSS values were completely reversed as compared to the ones in the simultaneous cueing condition and were shifted towards proximal visual stimuli. In other words, applying a nociceptive stimulus on one hand facilitated the perception of a visual stimulus presented in the close vicinity of the stimulated hand, irrespective of the distance of both the hands and the visual stimuli from the trunk. Our study extends the results of previous studies that evidenced the reverse effect, that is, the impact of visual stimuli on the perception of nociceptive stimuli, more specifically when the visual stimuli were presented close to the stimulated hand, independently of the distance of the hands relative to the trunk [3–5]. Similarly, other studies have pointed out the importance of the distance of the presented stimuli from the hand rather than its distance from the trunk by means of vegetative responses such as skin conductance responses (SCR) [22,23]. For instance, Rossetti et al. [22] observed that SCR to the occurrence of a threatening and potentially noxious stimulus was increased with the proximity of the stimulus to the hand, independently of its distance relative to the trunk.

One could argue that the impact of a nociceptive cue on visual perception could be due to a gaze shift triggered by the nociceptive stimulus towards its location, by increasing the foveal acuity of the spatially congruent visual stimuli. However, this hypothesis seems unlikely, since, due to the slow conduction velocity of the Aδ fibers (i.e. ~10 m/s), the time interval between the respective arrivals at the cortical level of the nociceptive and visual inputs is inferior to the duration of a saccade [24]. Our results are more

likely to support the existence of peripersonal representations of each limb that integrate somatic inputs, including nociceptive ones, and non-somatic inputs such as visual stimuli, when these visual stimuli are presented close to the limb. Moreover, our results support the idea that peri-limb representations play a primary role in nociceptive-visual interactions, while minimizing the effect of a more general peripersonal representation centered on the body as a whole. Such a conclusion is in line with similar studies investigating visuo-tactile interactions. For instance, single-cell recordings in monkeys have revealed the existence of bimodal neurons, mainly in the ventral parts of the premotor (vPM) cortex and the intraparietal sulcus (VIP) [19,25,26]. More specifically, some vPM neurons were found to associate both a tactile receptive field (RF) and a visual RF, with the particularity that the visual RF of these neurons is independent of the retina position, and is, instead, anchored to the tactile RF, moving with it during limb displacement. In humans, such peri-limb spatial representations were illustrated for instance by the behaviors of patients with extinction syndrome consecutive to right hemisphere damage characterized by an inability to report left-sided stimuli when presented simultaneously with right-sided stimuli. More specifically, the perception of a touch applied on one limb can be extinguished in these patients by a visual stimulus but only if it was presented close to the opposite and homologous limb [27]. In other words, patients' perceptual abilities were characterized by a pathologically unbalanced competition between spatial peripersonal representations of two specific homologous limbs (e.g. the two hands).

Our results are also of clinical relevance for the understanding of cognitive biases observed in chronic pain, such as complex regional pain syndrome (CRPS). CRPS is an affliction mainly characterized by pain, vegetative, motor and trophic symptoms in one limb. However, recent studies demonstrated a disrupted perception of tactile stimuli, which could not be explained by peripheral mechanisms,

but rather by a distortion of body representation [7]. Very recent studies have furthermore shown, using similar visual TOJ tasks, that CRPS patients can also display perceptual biases affecting the perception of external visual stimuli, especially those presented close to the affected limb, suggesting that they "neglected" the side of space around the affected limb [8]. Moreover, preliminary studies suggest that manipulating visuospatial perception combined with visuomotor coordination could be used as an efficient rehabilitation technique to alleviate pain and other related symptoms in CRPS [28]. Hence, studying interactions between nociception and vision could be useful to characterize the frames of reference involved in crossmodal interaction between pain and vision. This could lead to a better apprehension of the spatial representations potentially affected by chronic pain in order to improve the understanding of the pathophysiology of CRPS [7].

Acknowledgements

References

[1] G. Vallar, A. Maravita, Personal and extrapersonal spatial perception, in: G.G. Bernston, J.T. Cacioppo (Eds.), Handbook of Neuroscience for the Behavioral Sciences, Wiley, Hoboken, 2009, pp. 322–336.

[2] G. di Pellegrino, E. Làdavas, Peripersonal space in the brain, Neuropsychologia 66 (2015) 126–133.

[3] A.L. De Paepe, G. Crombez, C. Spence, V. Legrain, Mapping nociceptive stimuli in a peripersonal frame of reference: evidence from a temporal order judgment task, Neuropsychologia 56 (2014) 219–228.

[4] A.L. De Paepe, G. Crombez, V. Legrain, From a somatotopic to a spatiotopic frame of reference for the localization of nociceptive stimuli, PLoS One 10 (2015) e0137120.

[5] A.L. De Paepe, G. Crombez, V. Legrain, Remapping nociceptive stimuli into a peripersonal reference frame is spatially locked to the stimulated limb, Neuropsychologia (2017) (in press).

[6] C. Spence, C. Parise, Prior-entry: a review, Conscious. Cogn. 19 (2010) 364–379.

[7] V. Legrain, J.H. Bultitude, A.L. De Paepe, Y. Rossetti, Pain, body and space: what do patients with complex regional pain syndrome really neglect? Pain 153 (2012) 948–951.

[8] L. Filbrich, A. Alamia, C. Verfaille, A. Berquin, O. Barbier, X. Libouton, V. Fraselle, D. Mouraux, V. Legrain, Does complex regional pain syndrome impair the perception of body space and extra-body space (unpublished results, submitted).

[9] M.E.R. Nicholls, N.A. Thomas, T. Loetscher, G.M. Grimshaw, The Flinders handedness survey (FLANDERS): a brief measure of skilled hand preference, Cortex 49 (2013) 2914–2926.

[10] K. Inui, T. Tsuji, R. Kakigi, Temporal analysis of cortical mechanisms for pain relief by tactile stimuli in humans, Cereb. Cortex 16 (2006) 355–365.

[11] M. Churyukanov, L. Plaghki, V. Legrain, A. Mouraux, Thermal detection thresholds of $A\delta$- and C-fibre afferents activated by brief CO_2 laser pulses applied onto the human hairy skin, PLoS One 7 (2012) e35817.

[12] A. Mouraux, G.D. Iannetti, L. Plaghki, Low intensity intra-epidermal electrical stimulation can activate $A\delta$-nociceptors selectively, Pain 150 (2010) 199–207.

[13] L. Favril, A. Mouraux, C.F. Sambo, V. Legrain, Shifting attention between the space of the body and external space: electrophysiological correlates of visual-nociceptive crossmodal spatial attention, Psychophysiol 51 (2014) 464–477.

[14] L.L. Kontsevich, C.W. Tyler, Bayesian adaptive estimation of psychometric slope and threshold, Vis. Res. 39 (1999) 2729–2737.

[15] F.A.A. Kingdom, N. Prins, Psychophysics – A Practical Introduction, Elsevier Academic Press, London, 2010.

[16] C. Spence, D.I. Shore, R.M. Klein, Multisensory prior entry, J. Exp. Psychol. Gen. 130 (2001) 799–832.

[17] D. Cousineau, Confidence intervals in within-subject designs: a simple solution to Loftus and Masson's method, Tutor. Quant. Methods Psychol. 1 (2005), 45–45.

[18] L. Filbrich, A. Alamia, S. Burns, V. Legrain, Orienting attention in visual space by nociceptive stimuli: investigation with a temporal order judgment task based on the adaptive PSI method, Exp. Brain Res. 235 (2017) 2069–2079.

[19] M.S.A. Graziano, D.F. Cooke, Parieto-frontal interactions, personal space, and defensive behavior, Neuropsychologia 44 (2006) 845–859.

[20] J. Intrilligator, P. Cavanagh, The spatial resolution of visual attention, Cogn. Psychol. 43 (2001) 171–216.

[21] A.K.M.R. Karim, H. Kojima, The what and why of perceptual asymmetries in the visual domain, Adv. Cogn. Psychol. 6 (2010) 103–115.

[22] A. Rossetti, D. Romano, N. Bolognini, A. Maravita, Dynamic expansion of alert responses to incoming painful stimuli following tool use, Neuropsychologia 70 (2015) 486–494.

[23] D. Romano, M. Gandola, G. Bottini, A. Maravita, Arousal responses to noxious stimuli in somatoparaphrenia and anosognosia: clues to body awareness, Brain 137 (2014) 1213–1223.

[24] E.R. Kandel, J.H. Schwartz, T.M. Jessell, S.A. Siegelbaum, A.J. Hudspeth, Principles of Neural Science, 4th en., McGraw Hill, New York, 2013.

[25] G. Rizzolatti, C. Scandolara, M. Matelli, M. Gentilucci, Afferent properties of periarcuate neurons in macaque monkeys. II. Visual responses, Behav. Brain Res. 2 (1981) 147–163.

[26] J.-R. Duhamel, C.L. Colby, M.E. Goldberg, Ventral intraparietal area of the macaque: congruent visual and somatic responses properties, J. Neurophysiol. 79 (1998) 126–136.

[27] A. Farnè, M.L. Demattè, E. Làdavas, Neuropsychological evidence of modular organization of the near peripersonal space, Neurology 65 (2005) 1754–1758.

[28] D.M. Torta, V. Legrain, Y. Rossetti, A. Mouraux, Prisms for pain. Can visuo-motor rehabilitation strategies alleviate chronic pain? Eur. J. Pain 20 (2016) 64–69.