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Investigating the spatial characteristics of the crossmodal interaction between nociception and vision using gaze direction

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ABSTRACT

The present study investigated the influence of nociceptive stimuli on visual stimuli processing according to the relative spatial congruence between the two stimuli of different sensory modalities. Participants performed temporal order judgments on pairs of visual stimuli, one presented near the hand on which nociceptive stimuli were occasionally applied, the other one either to its left or to its right. The visual hemifield in which the stimulated hand and the near visual stimulus appeared was manipulated by changing gaze direction. The stimulated hemibody and the stimulated visual hemifield were therefore either congruent or incongruent, in terms of anatomical locations. Despite the changes in anatomical congruence, judgments were always biased in favor of the visual stimuli presented near the stimulated hand. This indicates that nociceptive-visual interaction may rely on a realignment of the respective initial anatomical representations of the somatic and retinotopic spaces toward an integrated, multimodal representation of external space.

1. Introduction

The cognitive mechanisms, and their neuronal substrates, underlying crossmodal interaction between somatic and non-somatic stimuli have been largely investigated over the last decades (see e.g. di Pellegrino & Làdavas, 2015; Holmes & Spence, 2004; Macaluso & Maravita, 2010). For such crossmodal interactions between somatic and non-somatic stimuli to be possible, one needs to be able to coordinate and to integrate the representation and the perception of the space of the body and those of its surrounding space. Conceptualized by the notion of peripersonal reference frames (Rizzolatti, Fadiga, Fogassi, & Gallese, 1997), such integrated and multisensory representations are coordinate systems for the spatial coding of both somatic and extra-somatic (e.g. visual) stimuli occurring near the body. Such systems are thought to be used as interfaces to translate the perceptual characteristics of an object near the body into a motor schema to spatially guide actions toward that object, such as grasping and dexterous manipulation (Brozzoli, Ehrsson, & Farne, 2014). It has been further hypothesized that such peripersonal representations could be used for the purpose of defensive actions against objects that threaten the physical integrity of the body (Cooke & Graziano, 2004; Graziano & Cooke, 2006). Supporting this latter hypothesis, recent studies in humans demonstrated a privileged interaction between visual stimuli occurring very close to the body, and nociceptive stimuli, that is, stimuli that selectively activate the nervous system specifically involved in coding and transmitting information about sensory events that have the potential to inflict body damage (see Legrain & Torta, 2015 for a review). Whereas the reference frames involved in tactile processing and the mechanisms underlying visuo-tactile interactions have been studied with a wide variety of tasks (e.g., di Pellegrino & Làdavas, 2015; Spence, Pavani, & Driver, 2004; Tamé, Wühle,

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Petri, Pavani, & Braun, 2017), most of the studies investigating visual-nociceptive interactions used temporal order judgment (TOJ) tasks. These tasks consist in presenting pairs of stimuli with various time delays between them, and participants have to report which of the two stimuli they perceived as having been presented first. In such tasks, the amount of time one stimulus has to follow or precede the other in order for the two stimuli to be perceived by the participant as occurring simultaneously is used as an index of attentional bias, and can be shifted to the advantage of one of the two stimuli (Spence & Parise, 2010). Indeed, according to the theory of prior entry (Titchener, 1908), paying attention to a stimulus speeds-up its processing as compared to a competing un-attended stimulus. A first series of experiments in which pairs of nociceptive stimuli were used, one applied on each hand dorsum, showed that judgments about the occurrence of nociceptive stimuli were dependent on the relative position of the hands in external space (De Paepe, Crombez, & Legrain, 2015; Sambo et al., 2013). When TOJ tasks were performed with the hands crossed over the midsagittal plane of the body, judgments were much less accurate, as compared to conditions in which the task was performed with a normal, uncrossed hand posture. These results suggest that the ability of perceiving nociceptive stimuli is not only determined by the anatomical position of the stimuli on the body, but also relies on frames of reference that integrate the relative position of the stimulated limb in external space (see Smania & Agliotti, 1995). Similar effects have been reported for tactile stimuli (Shore, Spry, & Spence, 2002; Yamamoto & Kitazawa, 2001). In further experiments, the nociceptive stimuli were preceded by a visual cue presented randomly in the same side of space as one of the hands (De Paepe, Crombez, Spence, & Legrain, 2014; De Paepe et al., 2015). These studies showed that the occurrence of the visual stimulus biased judgments in favor of the perception of the nociceptive stimuli applied on the hand laying in the same side of space as the visual stimulus. The effects were shown to be stronger for the visual stimulus presented the closest to the stimulated hand (De Paepe et al., 2014), independently of the relative position of the hands and the visual stimuli according to the participant's trunk (De Paepe et al., 2015). In other words, the ability of a visual stimulus to impact the perception of a nociceptive stimulus depends on the proximity of the visual stimulus to the limb on which the nociceptive stimulus is applied and thus on the location of the stimulated hand in external space, irrespective of the fact which hand was stimulated according to an anatomical reference (De Paepe et al., 2015). Taken together, these studies suggest the existence of a peripersonal frame of reference for the localization of nociceptive stimuli, thus enabling close visual stimuli in external space to affect the perception of nociceptive stimuli applied on the body.

There are longstanding debates on the mechanisms underlying crossmodal interaction between somatic and proximal non-somatic stimuli (Macaluso, Frith, & Driver, 2001; McDonald, Teder-Sälejärvi, & Ward, 2001; Spence, McDonald, & Driver, 2004). One of the most popular theories postulates that such interactions rely on the existence of neurons able to respond to both somatic and non-somatic stimuli (see Graziano, Gross, Taylor, & Moore, 2004 for a review). More precisely, electrophysiological studies in monkeys have revealed, mostly in the ventral premotor cortex (PMv) and ventral intraparietal sulcus (VIP), the existence of neurons associating tactile and visual receptive fields (RFs). The particularity of these visual RFs is that they are often limited and anchored to the body parts which *host* their associated tactile RFs, thus following these limbs during their movements in space. In other words, the tactile and the visual RFs are aligned according to a frame of reference that takes into account external space, instead of their initial and respective anatomical frames of reference (i.e. somatotopic and retinotopic, respectively). Several studies have shown, for instance, that PMv neurons respond to both visual and tactile stimuli only when the position or the trajectory of the visual stimulus is spatially congruent with the limb that hosts the RF of the tactile stimulus, irrespective of the posture of the body and the projection of the visual stimulus onto the retina (Fogassi et al., 1992, 1996; Gentilucci, Scandolara, Pigarev, & Rizzolatti, 1983; Graziano, Hu, & Gross, 1997; Graziano, Yap, & Gross, 1994). Indeed, Graziano et al. (1997) have shown that visual stimuli were still able to activate such bimodal neurons even when the monkeys were trained to fixate their gaze at different positions. Similar effects have been observed in neuroimaging studies performed in humans (see Macaluso & Maravita, 2010). For instance, Macaluso and colleagues investigated how cortical responses to a stimulus of one sensory modality can be influenced by the proximal occurrence of a stimulus of another sensory modality (Macaluso, Frith, & Driver, 2000, 2002). In one of their studies, participants were asked to place one hand, on which tactile stimuli were applied, close to a visual stimulus, and, across conditions, to fixate their gaze either to the left or to the right of the visual stimulus and the stimulated hand (Macaluso et al., 2002). Using such a manipulation, the visual stimulus was alternately seen in different visual hemifields, while the tactile stimulus was always felt on the same hemibody. The occurrence of a tactile stimulus was shown to boost the cortical responses to the visual stimuli in the visual cortex contralateral to visual stimuli location, independently of the primary cortical projection of the tactile input to its contralateral hemisphere, and thus irrespective of the hemispheric correspondence between the visual and the tactile cortical projections (Macaluso et al., 2002).

The studies reviewed here above suggest that one of the mechanisms underlying crossmodal interaction between somatic and non-somatic stimuli relies on the ability to update the mapping coordinates from the initial anatomical reference frames of each sensory modality (i.e. somatotopic for somatosensory inputs and retinotopic for visual inputs) to an integrated mapping system using external space as main reference frame. They also suggest that such an updating takes into account the relative position of the limbs and the eyes, whatever the stimulated hemibody and hemifield. In the present study, we investigated whether nociceptive stimuli can influence the perception of visual stimuli, especially those presented close to the limb on which the nociceptive stimuli are felt. This question is of particular importance when considering that it has been suggested that chronic pain states could change how patients perceive their visual environment (see e.g. Legrain, Bultitude, De Paepe, & Rossetti, 2012). More specifically, we investigated whether such an interaction between nociceptive and visual stimuli depends on the relative spatial congruence between the location of the nociceptive stimuli (i.e. of the stimulated limb) and that of the visual stimuli, irrespective of their exact positions according to their respective sensory RFs (i.e. the congruence of their respective anatomical reference frames). To this end, we manipulated the direction of the gaze so that visual stimuli and the body part on which nociceptive stimuli were applied could be seen in different areas of the visual field, while the cortical projections of the nociceptive inputs remained constant (as it was always the same limb that was stimulated). Participants performed TOJs on pairs of visual stimuli, one centrally positioned in front of the participant and

one more laterally. One of the hands was placed close to the central visual stimulus, and nociceptive stimuli could occasionally be applied on that specific hand. Using such a setting, the central visual stimuli were therefore always the ones spatially congruent with the nociceptive stimuli. However, by changing gaze direction across the experimental blocks, central visual stimuli could either appear as left-sided stimuli (i.e. in the left visual hemifield) when participants' gaze was shifted toward the right side of space, or as right-sided stimuli (i.e. in the right visual hemifield) when gaze was shifted to the left side. We hypothesized that if nociception influences vision based on their spatial correspondence in external space, nociceptive stimuli would bias visual TOJs in favor of the perception of the visual stimuli presented close to the stimulated hand, i.e., the centrally positioned visual stimuli, independently of left vs. right gaze direction. In other words, the visual hemifield (left vs. right) that would be prioritized by the occurrence of the nociceptive stimuli should be reversed as function of the change in gaze direction. Such a result would also corroborate the hypothesis that somatic, including nociceptive, and non-somatic stimuli are remapped from their respective initial frames of reference into a common frame that uses the space around the body as reference.

2. Methods

2.1. Participants

Twenty volunteers (14 women, mean age: 23.15 ± 3.91 years, range: 20–38 years) took part in the experiment. Exclusion criteria were non-corrected vision deficits, neurological, psychiatric, cardiac or chronic pain problems, regular use of psychotropic drugs, as well as a traumatic injury of the upper limbs within the six months preceding the experiment. The use of any analgesic substances (e.g. NSAIDs or paracetamol) within the 12 h preceding the experiment was not allowed. Participants were asked to sleep at least 6 h the night before the experiment. Eighteen participants were right-handed, one participant was left-handed and one participant ambidextrous (Flinders Handedness Survey (Flanders), Nicholls, Thomas, Loetscher, & Grimshaw, 2013). The experimental procedure was approved by the local ethics committee (Commission d'Ethique Biomédicale Hospitalo-Facultaire of the Université catholique de Louvain) in agreement with the latest version of the Declaration of Helsinki and was carried out in accordance with the corresponding guidelines and regulations. Written informed consent was obtained prior to the experimental session and participants received financial compensation for their participation.

2.2. Stimuli and apparatus

Nociceptive stimuli were applied using intra-epidermal electrical stimulation (IES) (with a DS7 Stimulator, Digitimer Ltd, UK) by means of a stainless steel concentric bipolar electrode (Nihon Kohden, Japan; Inui, Tsuji, & Kakigi, 2006) consisting of a needle cathode (length: 0.1 mm, Ø: 0.2 mm) surrounded by a cylindrical anode (Ø: 1.4 mm). To guarantee the selective activation of Aδ nociceptors, without co-activation of Aβ mechanoreceptors, the following procedure was followed to apply IES (see Mouraux, Iannetti, & Plaghki, 2010; Mouraux, Marot, & Legrain, 2014; Mouraux et al., 2013). The electrodes were gently pressed against the skin of the hand dorsum to insert the needle in the epidermis of the sensory territory of the superficial branch of the radial nerve. Absolute detection thresholds to a single 0.5 ms square-wave pulse were determined using a staircase procedure (Churyukanov, Plaghki, Legrain, & Mouraux, 2012). The intensity of the electrical stimulation was then individually set to twice the absolute detection threshold, with a limit of 0.5 mA. To guarantee that intensities were perceived equivalently between both hands, they could be individually adjusted if necessary (see Favril, Mouraux, Sambo, & Legrain, 2014 for details). During the experiment, stimuli consisted of trains of three consecutive 0.5 ms square-wave pulses separated by a 5 ms interpulse interval (Mouraux et al., 2013, 2014). The sensation was described as pricking but not necessarily painful. The level of perceived intensity of the nociceptive stimuli at twice the detection threshold was assessed for each hand using a scale from 0 to 10, with 0 = no sensation and 10 = very intense sensation.

Three white light emitting diodes (LEDs) with a 17 lm luminous flux, a 6.40 cd luminous intensity and a 120° visual angle (GM5BW97330A, Sharp Corporation, Japan) served as visual stimuli. They were perceived as brief flashes. Two yellow LEDs (min. 0.7 cd luminous intensity at 20 mA, 120° viewing angle; Multicomp, Farnell element14, UK) served as fixation points during the task.

2.3. Procedure

Participants were tested in a dimly-illuminated testing room, sitting in front of a table. In order to minimize head movements, their heads were stabilized with a chin-rest placed ∼10 cm from the trunk. The three white LEDs were fixed on the table. One LED was placed centrally (centered on the chin rest), ∼50 cm in front of the participants (central LED), one LED ∼40 cm to the left of the centrally placed LED (left LED), and one LED ∼40 cm to the right of the centrally placed LED (right LED). One yellow fixation LED was placed equidistantly between the left LED and the central LED (left fixation) and another one equidistantly between the central LED and the right LED (right fixation). All the LEDs were aligned on a single line parallel to the edge of the table where the participants were seated. The participants placed one single hand (either the left or the right one, counterbalanced between participants), palm down, next to the central LED, with a maximum distance of 1 cm between the LED and the metacarpophalangeal joint of the index finger (see Fig. 1). We chose to counterbalance the stimulated hand between participants rather than to stimulate both hands alternately in all participants to avoid extending the experiment duration excessively and introducing confounding task-independent attention shifts and fatigue that could interfere with the perceptual effects we aim to study.

Before each experimental block, participants were told whether to fixate their gaze at the left or the right fixation LED – without
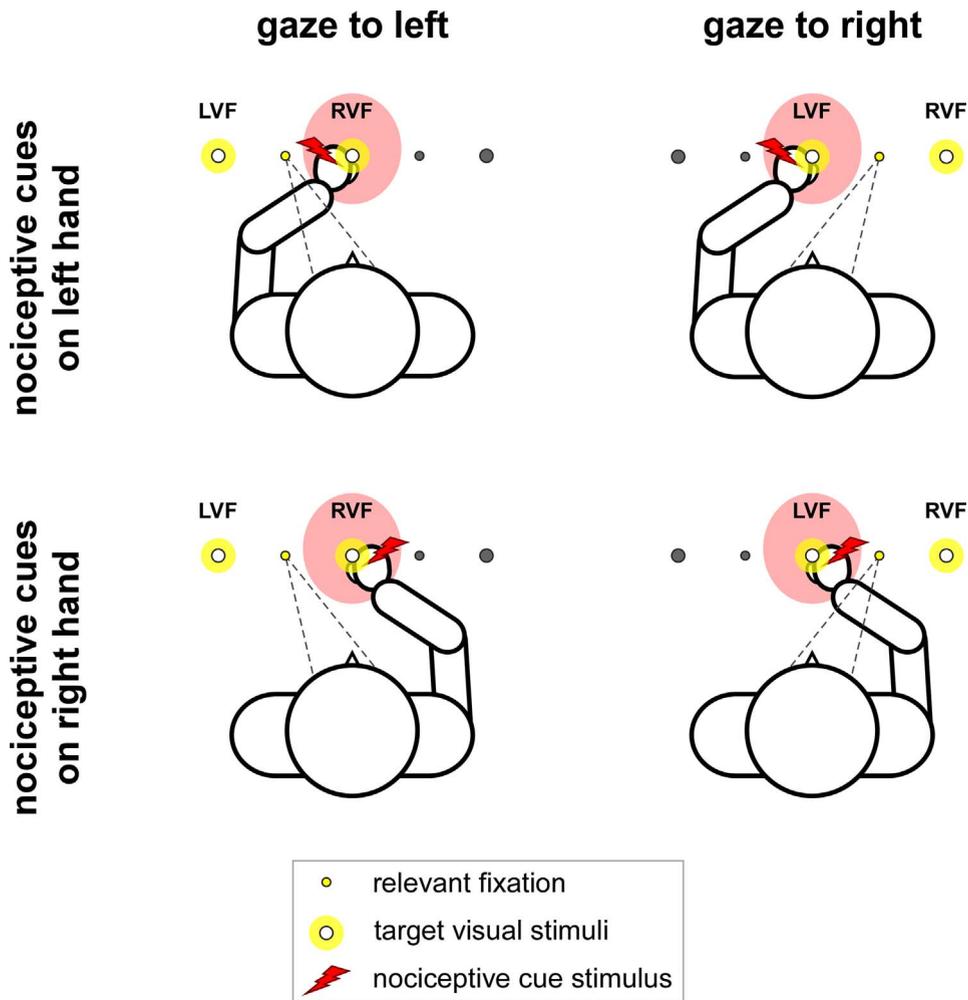
Fig. 1. Design of the experiment. Visual stimuli are presented by means of three white LEDs, one placed centrally in front of the participants and two other ones, one placed to the left and one placed to the right of the central LED. The task-relevant pair for each condition is represented by the white circles with a small yellow halo, and always consists in a visual stimulus seen in the left visual hemifield (LVF) and a visual stimulus seen in the right visual hemifield (RVF). Either the left or the right hand, counterbalanced between participants, is placed next to the central LED. Nociceptive cues are illustrated by the red flashes, and are occasionally applied on the centrally placed hand, shortly preceding the visual stimuli. Depending on the condition, participants either fixated their gaze, without moving their head, at a left or a right fixation point, which are both represented by the yellow circles. Accordingly, the potentially stimulated hand is either seen in the RVF or in the LVF, respectively. The LED expected to be prioritized during TOJs in the different conditions is encircled by the large rose halo. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

moving their head – so that the central LED and the hand on which nociceptive stimuli could be applied were either seen in the participants' right visual hemifield (RVF) in case of left fixation, or in their left visual hemifield (RVF) in case of right fixation. A trial started with the illumination of the fixation LED and after 500 ms, participants either received a nociceptive stimulus applied on the hand (cue condition) or no stimulation (no cue condition). The condition without nociceptive stimulation was introduced to control for effects on visual perception due to the mere presence of a hand that could potentially attract attention to its position (e.g. Lloyd, Azanon, & Poliakoff, 2010; Reed, Grubb, & Steele, 2006) instead of the nociceptive cues. Two hundred ms (Filbrich, Alamia, Burns, & Legrain, 2017b) after the potential onset of the nociceptive stimulation, a pair of visual stimuli (the left LED and the central LED in case of left fixation or the central LED and the right LED in case of right fixation), both stimuli of 5 ms duration each, was presented. Twenty possible time intervals (SOAs, i.e. stimulus onset asynchronies) were used between the two visual stimuli: ± 200, ± 145, ± 90, ± 75, ± 60, ± 45, ± 30, ± 15, ± 10, ± 5 ms (negative values indicate that the LED in the LVF was illuminated first, positive values that the one in the RVF was illuminated first). Participants were instructed to keep their gaze at the fixation point during the whole trial. Depending on the block, they either reported verbally which of the two visual stimuli they perceived as appearing first, or they reported which visual stimulus they perceived as appearing second (by answering '*left*' or '*right*', corresponding to the LVF and the RVF, respectively). Using these two response modalities allows minimizing the contribution of response and/or decision-related biases to the perceptual spatial biases that are investigated (for details see e.g. Filbrich, Torta, Vanderclausen, Azanon, & Legrain, 2016; Shore, Spence, & Klein, 2001; Spence & Parise, 2010). The participants didn't receive any specific instruction regarding

response speed, as well as no feedback regarding the accuracy of their performance. Illumination of the fixation point was switched off as soon as the response was encoded by the experimenter and the next trial started 2000 ms later. A rest period between the blocks was possible when requested. Duration of the whole experiment was approximately 45 min.

Participants started with a practice session of two blocks of 10 trials each (either two blocks of left fixation or two blocks of right fixation, one block per response modality) only with the two highest SOAs. The experimental session was composed of four blocks resulting from the combination of the gaze direction (left vs. right) and the response factors ('which is first' vs. 'which is second'). The order of the blocks was randomized. Each block consisted of two series of 30 trials, one for each nociceptive cue condition (cue vs. no cue). The trials of the two different series were equiprobably intermixed and presented in random order. Since we used an adaptive method to vary the different SOAs between the two visual stimuli (i.e. the adaptive PSI method, Kontsevich & Tyler, 1999), the SOA that was actually presented at a trial (out of the 20 possible SOAs) was determined online, i.e. based on the participants' performance on all previous trials within one cue condition (implemented through the Palamedes Toolbox, Prins & Kingdom, 2009).

After each block, levels of perceived intensity of the nociceptive stimuli were again assessed (on a scale from 0 to 10, with 0 = no sensation and 10 = very intense sensation), to ensure that they were still perceived. If this was not the case, the intensity was adapted, or the electrode displaced and the absolute threshold measurements restarted (see Favril et al., 2014 for details). For further analyses, the stimulus intensity used for each participant was characterized by the highest intensity of current adjusted during the experiment.

2.4. Measures

To assess the performance of the participants in the TOJ task we consider two measures: the point of subjective simultaneity (PSS) and the slope. In the present study, these two measures were estimated as the α and β parameters of a logistic function, i.e. $f(x) = \frac{1}{1 + \exp(-\beta(x - \alpha))}$, respectively, which was fitted to the data for each participant and each condition. The α defines the threshold of the psychometric function. In our study, this threshold corresponds to the SOA at which the two visual stimuli are perceived as occurring first equally often (i.e. the 0.5 criterion on the ordinate). Accordingly, this measure corresponds to the PSS which is defined as the amount of time one stimulus has to precede or follow the other in order for the two stimuli to be perceived by the participant as occurring simultaneously (Spence, Shore, & Klein, 2001). The β parameter defines the slope of the logistic function, which describes the noisiness of the results and can be related to the precision, i.e. variability, of the participants' responses during a condition (Kingdom & Prins, 2010). The psychometric curve and its parameters were estimated at each trial, since we used the adaptive PSI method (Kontsevich & Tyler, 1999) to adapt the experimental procedure and the presented SOAs, which is based on an algorithm that adopts a Bayesian framework (for a detailed description of how the logistic function is estimated and the advantages of using the adaptive PSI method in TOJ, see Filbrich et al., 2017b).

For both left and right gaze direction conditions, the proportion of trials in which the visual stimulus presented in the LVF was reported as appearing first was plotted as a function of SOA.

2.5. Data analysis

The means of the maximal intensity of the nociceptive stimuli were compared between left and right hands using an independent-samples *t*-test. Means of self-reported perceived intensities of the nociceptive stimuli registered directly after the threshold measures and before the first block, as well as of the mean of perceived intensities across blocks were compared between the left and right hand using a Mann-Whitney test for independent samples. Before statistical analyses of the TOJ task, data from the two response modalities ('which is first' vs. 'which is second?') were merged to reduce the contribution of potential response biases. To characterize potential shifts in TOJs to one visual hemifield in the different experimental conditions, one-sample t-tests comparing each PSS value to 0 were performed. Differences across conditions for PSS and slope values were tested using an analysis of variance (ANOVA) for repeated measures with *cue condition* (cue vs. no cue) and *gaze direction* (left vs. right) as within-participant factors, as well as *hand* (left vs. right) as between-participant factor. Greenhouse-Geisser corrections of degrees of freedom and contrast analyses were used when necessary. Significance level was set at p ≤ .05. Effect sizes were measured using Cohen's d for t-tests or partial Eta squared for ANOVAs.

3. Results

3.1. Intensity of nociceptive stimuli

The mean of the maximal intensities was 0.30 ± 0.09 mA for nociceptive stimuli applied to the right hand and 0.30 ± 0.11 for nociceptive stimuli applied to the left hand (no significant difference: $t(18) = 0.00$, $p = 1$). These intensities are in the range of values that have been shown to selectively activate skin nociceptors in previous studies (Mouraux et al., 2010, 2013, 2014). The means of the self-reported intensities before the first block were 5.4 ± 2.17 and 5 ± 2.31 for the right and the left hand, respectively (no significant difference: $U = 46.5$, $p = .796$). Means of the self-reported mean intensities across the four blocks were 4.72 ± 2.18 and 4.32 ± 2.04 for the right and the left hand, respectively (no significant difference: $U = 46.5$, $p = .796$).
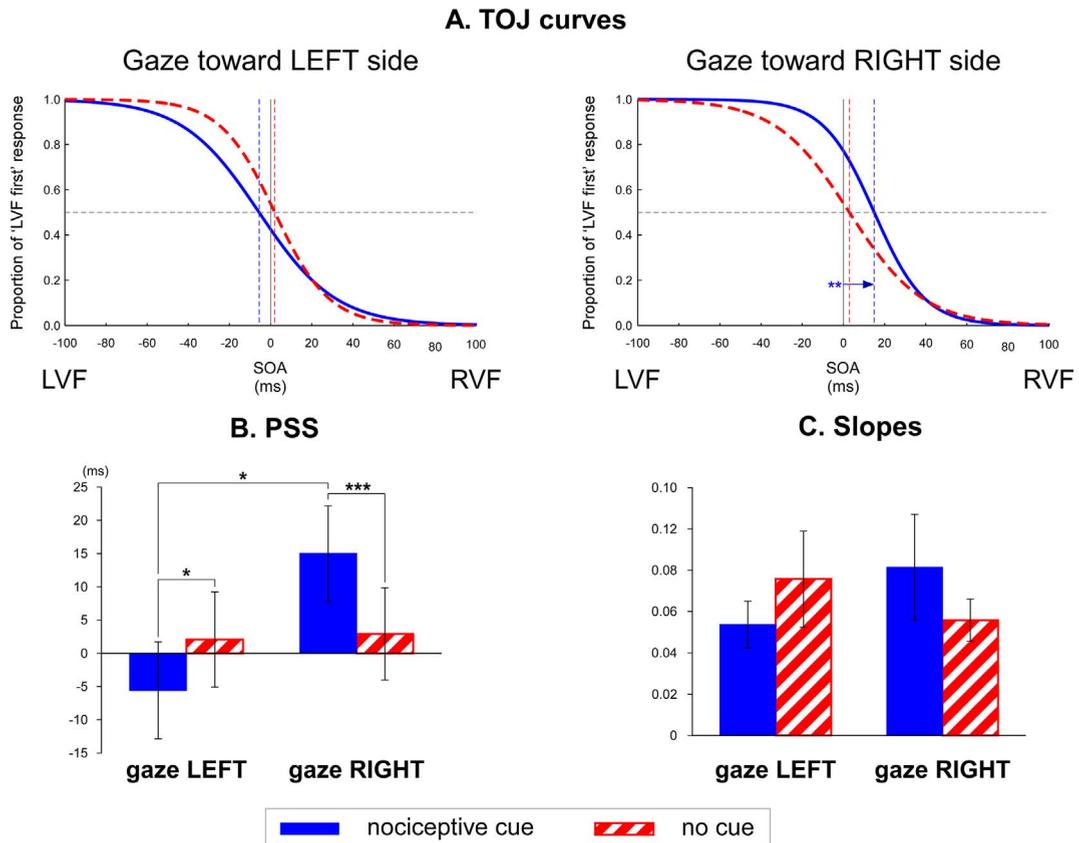
Fig. 2. Averaged results of the 20 participants. The upper part of the figure (A) depicts the fitted logistic functions for the *left gaze direction* and the *right gaze direction* conditions. The x-axis represents different hypothetical stimulus onset asynchronies (SOAs) between the two visual stimuli: negative values indicate that the visual stimulus in the left visual hemifield (LVF) was presented first, while positive values indicate that the visual stimulus in the right visual hemifield (RVF) was presented first. The y-axis represents the proportion of trials in which the participants perceived the visual stimulus in the LVF as occurring first. For both left gaze direction and right gaze direction conditions, red dashed curves represent the conditions in which no nociceptive cue was applied on the centrally placed hand, with the corresponding PSS values indicated by the red vertical dashed lines. Blue solid curves represent the conditions in which a nociceptive cue was applied on the hand, with the corresponding PSS values indicated by the blue vertical dashed lines. The blue arrow in the *right gaze direction* condition indicates the PSS value significantly different from zero. In this condition, when a nociceptive cue was applied, curves are shifted to the RVF, indicating that visual stimuli presented in the RVF had to be presented several ms before the visual stimuli presented in the LVF (i.e. the one spatially congruent with the stimulated hand) to have the chance to be perceived as occurring first equally often. The lower parts of the figure illustrate the mean PSS (B) and slope (C) values, for both the *left gaze direction* and the *right gaze direction* conditions. Significant differences are indicated with asterisks (*p ≤ .05, **p ≤ .01, ***p ≤ .001). Error bars represent the 95% confidence intervals adapted according to the method of Cousineau (2005). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2. PSS

Results are illustrated in Fig. 2. In the conditions with nociceptive cue, one-sample t-tests showed that PSS values were positive (14.99 ± 20.23) and significantly different from zero ($t(19) = 3.31$, $p = .004$, $d = 0.74$) when gaze was directed to the right (and, therefore, central LED and hand in the LVF). However, when gaze was directed to the left (central LED and hand in RVF), PSS values tended to be more negative ($-5.57 ± 20.43$) but not significantly different from 0 ($t(19) = -1.22$, $p = .283$). For the no cue condition, neither PSS values for the left gaze direction nor for the right gaze direction were significantly different from zero (all $t(19) ≤ 0.81$, $p ≥ .43$). When gaze was directed to the right, visual stimuli appearing in the RVF (i.e. the uncued side of space) had thus to be presented significantly earlier than stimuli appearing in the LVF (i.e. the cued side of space) to have the chance to be perceived as occurring simultaneously.

The ANOVA revealed a significant interaction between *cue condition* and *gaze direction* ($F(1,18) = 18.06$, $p ≤ .001$, $\eta_p^2 = 0.50$). Contrast analyses showed that, during left fixation, the PSS value was significantly smaller in the cue than in the no cue condition ($F(1,19) = 5.62$, $p = .029$, $\eta_p^2 = 0.23$). On the contrary, during right fixation, the PSS value was significantly larger in the cue than in the no cue condition ($F(1,19) = 18.13$, $p ≤ .001$, $\eta_p^2 = 0.49$). In addition, the PSS values of the cue conditions were significantly different between left and right fixation conditions ($F(1,19) = 9.65$, $p = .006$, $\eta_p^2 = 0.34$), whereas such a comparison revealed quite identical values in the no cue conditions ($F(1,19) = 0.02$, $p = .90$, $\eta_p^2 = 0.00$). In the conditions during which nociceptive stimuli were applied on the hand, spatial biases changed direction according to gaze fixation: when the gaze was directed to the left, temporal order was judged to the advantage of stimuli in the RVF, whereas it was judged to the advantage of stimuli in the LVF when

gaze was directed to the right. In other words, judgments were always biased to the advantage of the visual stimuli the closest to the hand on which the nociceptive stimuli were applied, irrespective of the visual hemifield in which they were seen. The between-participant factor *hand* was also significant ($F(1,18) = 7.55$, $p = .013$, $\eta_p^2 = 0.30$), suggesting that biases were larger when the left hand (M = 10.30, SD = 23.05) was placed next to the central LED than when the right hand (M = −3.09, SD = 15.90) was placed there. None of the main effects and no interaction with the between-participant factor were significant (all $F \leq 3.07$, $p \geq .097$).

3.3. Slope

Results are illustrated in Fig. 2. The ANOVA revealed a significant interaction between *cue condition* and *gaze direction* (F(1,18) = 8.17, $p = .010$, $\eta_p^2 = 0.31$). None of the main effects or any of the interactions with the between-participant factor *hand* were significant (all $F \leq 1.96$, $p \geq .178$). However, none of the contrasts we performed could explain the *cue x gaze direction* interaction (all $F \leq 2.81$, $p \geq .101$). This suggests that the precision of the participants' responses does not seem to be affected differently neither in the left vs. right fixation condition as a function of cue condition, nor in the cue vs. no cue conditions as a function of gaze direction.

4. Discussion

The aim of the present experiments was to study the effect of the spatial alignment between nociceptive and visual stimuli according to the relative spatial position of their respective receptive fields on nociceptive-visual interactions. Such effects of spatial alignment have usually been investigated using the crossed-hands procedure during which stimuli are applied when the hands are crossed over the body midline (e.g. De Paepe et al., 2015; Eimer, Cockburn, Smedley, & Driver, 2001; Kennett, Eimer, Spence, & Driver, 2001; Kennett, Spence, & Driver, 2002; Shore et al., 2002; Yamamoto & Kitazawa, 2001). Using such a procedure, the left and right sides of space are defined for both somatic and extra-somatic stimuli according to a trunk-based reference. Hence, hemispaces (for extra-somatic stimuli) and hemibodies (for somatic stimuli) are defined according to the same reference axis (i.e. the trunk/head). Here, we investigate the effects of spatial alignment by manipulating current gaze direction. Manipulating gaze direction could be considered as being slightly different from the classical crossed-hands procedure, in the sense that, with this procedure, the representations of the different stimuli in terms of left vs. right side of space can be defined according to different reference axes. Indeed, whereas the visual stimuli and the stimulated hand were either seen in the left or the right hemifield (i.e. hemispace) according to an eye-centered reference, the stimulated hemibody (i.e. the hand) was still defined according to a reference centered on the trunk. Consequently, manipulating gaze direction while keeping the position of the head constant entails that in some trials spatially congruent nociceptive and visual stimulations occur in one visual hemifield, while in other trials such spatially congruent multimodal stimulations occur in the opposite hemifield according to an eye-centered reference, despite the fact that the physical positions of the visual stimuli and the hand on which the nociceptive stimulus was applied remain unchanged according to a trunk-centered reference (see Macaluso et al., 2002 for a similar procedure with tactile stimuli). In the present study, we aimed to demonstrate that the influence of nociception on visual perception is strongest when nociceptive and visual stimuli are congruent in external space, i.e. seen in the same hemifield, independently of the direction of gaze, and independently of the anatomical congruence between the stimulated hemibody and the stimulated visual hemifield. This hypothesis was tested by using TOJ tasks. In the present experiment, shifts of the PSS in the perception of visual stimuli were aimed to be induced by nociceptive cues presented in one side of space. Results showed that for both gaze direction conditions, biases were more important in the conditions with a nociceptive cue than in conditions without nociceptive cue, suggesting that a nociceptive stimulus can impact visual perception. Importantly, when a nociceptive cue was applied on the centrally placed hand, the direction of the bias changed according to the gaze direction, showing that participants' TOJs prioritized the perception of visual stimuli presented in the RVF when gaze was directed to the left (i.e. the stimulated hand is seen in the RVF), whereas they prioritized the perception of visual stimuli presented in the LVF when gaze was directed to the right (i.e. the stimulated hand is seen in the LVF). Thus, participants always prioritized the visual stimuli presented close to the stimulated hand, irrespective of the gaze direction.

It has to be noted however that, even if there was a significant difference in the biases between conditions with cue and conditions without cue for both left and right gaze conditions, biases to the advantage of visual stimuli presented close to the nociceptive stimulus in the cue conditions were only significantly different from zero when gaze was directed to the right (i.e. when the stimulated hand was seen in the LVF). This could be explained by a slight *general* bias to the LVF that would even be present when spatial attention is not explicitly manipulated by the presence of nociceptive cues. Such systematic left-ward biases in visuospatial attention, termed *pseudoneglect*, are a well-described phenomenon in neurologically intact participants (see e.g. Bowers & Heilman, 1980; Brooks, Della Sala, & Darling, 2014; Jewell & McCourt, 2000; Voyer, Voyer, & Tramonte, 2012). Although the left-ward biases in the no cue condition were not significantly different from zero, one could still imagine a possible influence on the crossmodal effects. Such a *general* bias to the LVF could enhance biases to the advantage of the visual stimulus in the LVF, induced by the spatial correspondence of the nociceptive stimulus in the same hemifield, when gaze was directed to the right, while it could reduce biases to the advantage of the RVF, induced by the presence of the nociceptive stimulus in the same hemifield, when gaze was directed to the left. Importantly however, we showed that a nociceptive stimulus seen in the RVF can induce biases to the advantage of visual stimuli in the RVF, thus counterbalancing the possible influence of a *general* bias to the LVF (by changing the direction of the bias). Thus, even if biases to the advantage of the visual stimuli presented close to the stimulated hand (in the RVF) when gaze was directed to the left were not significantly different from zero, this finding doesn't change the fact that we were able to demonstrate that the

perception of a visual stimulus can be impacted by a nociceptive stimulus applied on a hand that is seen in the same hemifield, that is, when both stimuli are presented in the same location in external space.

It could also be argued that, in the conditions in which no nociceptive cue was applied on the hand, visuospatial biases could have been induced by the fact that participants could still have expected/anticipated the application of a nociceptive stimulus on the hand, since nociceptive stimuli were always applied on the same hand (for the same participant). Indeed, it has been suggested that anticipating pain at a particular body location could prioritize sensory input at that location (Vanden Bulcke, Crombez, Durnez, & Van Damme, 2015; Vanden Bulcke, Van Damme, Durnez, & Crombez, 2013). Since biases in the conditions without nociceptive cue were not significantly different from zero, the possibility of anticipating a nociceptive stimulus seems not to have contributed predominantly to the results, but a certain influence, e.g. by reducing the significance of the comparison between cue vs. no cue conditions, can however not be excluded.

An unexpected result was the main effect of the between-participant factor *hand*, showing that visuospatial biases were of larger magnitude when the nociceptive stimulus was applied on the left hand than when it was applied on the right hand. This factor did however not interact with the other manipulated variables of the experiment. Accordingly, the difference between biases induced by nociceptive stimuli applied on the left vs. right hand seems not due to the main experimental manipulation in this study, i.e. gaze shift - possible interpretations of this effect should thus be considered within a larger framework and are beyond the scope of the present study.

It is interesting to note that recent studies in chronic pain patients also demonstrated visuospatial biases in perceiving near visual stimuli that seem related to the painful limb. By using a similar TOJ task with visual stimuli as in the present study, Filbrich et al. (2017c) showed that patients suffering from complex regional pain syndrome judged temporal order to the disadvantage of visual stimuli that were presented in the same side of space as the affected limb (see also Bultitude, Walker, and Spence (2017) for similar results). Importantly, such visuospatial biases were primarily evidenced when visual stimuli were presented in the direct vicinity of the affected limb. Although there are similarities between the present study and these latter findings in CRPS patients, it is however difficult to generalize our findings to a context of chronic pain, since the nociceptive stimuli used in the present study can hardly be compared to the presence of continuous chronic pain. Additionally, we showed that the nociceptive stimulus *facilitates* the processing of the near visual stimulus, whereas patients suffering from chronic pain seem to have *deficits* in processing visual stimuli that occur close to the painful limb. Nevertheless, combining the present results with the findings in chronic pain patients allows drawing a relatively coherent picture, with nociception and pain being able to influence how we perceive our close visual surroundings.

One might wonder whether the effects of the spatial alignment between nociceptive and visual stimuli in external space can also be observed when the stimulated hand is not visible. Our data does indeed not allow dissociating whether the observed crossmodal influence of nociceptive stimuli on visual judgments depends on the seen position of the stimulated hand (i.e. visual cue from the hand) or rather on its felt position (i.e. proprioceptive cue). This question has already been addressed in the context of visuo-tactile crossmodal interactions. On the one hand there are studies that have shown that the processing and perception of visual stimuli can be influenced by spatially congruent tactile stimuli even if the stimulated hand is unseen (Kennett et al., 2002; Macaluso et al., 2002; Mattingley, Driver, Beschin, & Robertson, 1997). On the other hand, the results of these latter studies contrast with those from studies that investigated the reverse link, i.e. the crossmodal influence from visual stimuli on tactile perception, and which directly compared visible vs. invisible hand conditions (e.g. Ladavas, Farnè, Zeloni, & di Pellegrino, 2000; Maravita, Spence, Sergent, & Driver, 2002; Pavani, Spence, & Driver, 2000). Indeed, these studies showed that the processing and perception of tactile stimuli is mostly impacted by the occurrence of spatially congruent visual stimuli when the hand (even a fake one, see Pavani et al., 2000) is visible (see also Gallace & Spence, 2005; Soto-Faraco, Ronald, & Spence, 2004, for studies that demonstrated a predominance of vision over proprioception when both are dissociated in the context of tactile processing). Based on these findings for the tactile modality, one could hypothesize that establishing spatial alignment between nociceptive and visual stimuli in external space predominantly depends on visual information rather than on proprioceptive inputs about the position of the stimulated hand. Furthermore, considering that it has been proposed that the accuracy in determining hand position diminishes substantially in the absence of visual information (see Holmes, 2013), one could hypothesize that if people are less accurate in determining hand position in the absence of vision, it could also be less evident for them to perceive that the nociceptive stimulus applied on the hand and the visual stimulus presented close to the hand are proximal in external space. However, one should also bear in mind that the dominant role of visual information over proprioceptive one might depend on the direction of the crossmodal influence.

One limitation of the present experimental design is that we did not monitor whether the participants kept their gaze at the fixation LED throughout the trials. It could thus be argued that the described biases to the advantage of visual stimuli presented next to the stimulated hand could be simply due to a facilitated processing of the visual stimulus in the foveal region, induced by a displacement of gaze toward the location of the nociceptive stimulus. However, considering the experimental timing and the type of nociceptive stimulation used in the present experiments, this seems rather unlikely. Indeed, IES activates specifically finely myelinated Aδ-fibers that convey nociceptive inputs with a slow conduction velocity (Purves et al., 2012). Accordingly, the nociceptive input takes at least 150 ms to reach the cortical level (see also Filbrich et al., 2017b). Since the time interval between the onset of the nociceptive cue and the first visual stimulus is 200 ms, this would only leave a time-window that is inferior to the duration of an eye movement to be initiated and executed to the stimulated hand (Purves et al., 2012). Therefore, the visual stimuli would appear before the actual displacement of the gaze. It seems thus not likely that the effects we observed were due to shifts in overt attention to the hand on which the nociceptive stimulus was applied. Furthermore, we also attempted to minimize eye-movements during a trial by switching off the fixation LED after the participant's response and switching it on again before the next trial, which allowed recapturing the participant's attention toward the fixation.

The question raised in the present study, i.e. whether nociception influences visual perception based on their spatial

correspondence in external space, can be considered in the more general context of studying the spatial nature of spatially specific crossmodal influences between stimuli of different sensory modalities. For instance, visual stimulus location is initially represented in retinal coordinates, whereas somatosensory (i.e. tactile or nociceptive) stimulation is initially represented in somatotopic coordinates. When the eyes move or arm posture is changed, the spatial alignment of these two representations will change relatively to each other (Macaluso & Maravita, 2010). In studies investigating crossmodal interactions between touch and vision, for instance, the spatial relation between tactile and visual stimuli is often fixed (see e.g. Macaluso et al., 2000), with a right tactile stimulation always occurring in the RVF or a left tactile stimulation always occurring in the LVF. In these studies, effects of spatial congruence on crossmodal visuo-tactile influence could be due to bimodal stimulation of the same hemisphere or to the spatial alignment of tactile and visual stimuli in external space. The former case implies that irrespective of the position of the tactile and visual stimuli in external space, a tactile stimulus applied on the left hand, for instance, always interacts with visual stimuli presented in the LVF because both modalities activate the same hemisphere. The latter case implies that a tactile stimulus applied on the left arm can either interact with visual stimuli in the LVF or visual stimuli in the RVF, depending on the current position of the hand with regard to the retina, suggesting that, for instance, information regarding current posture is taken into account to update the mapping between spatial representations for different sensory modalities that initially use different coordinate systems (Macaluso et al., 2002). For the tactile modality, these two accounts of the spatial nature of spatially specific crossmodal interactions have been disentangled by manipulating the alignment of tactile and visual reference frames, i.e. by dissociating the position of the sensory inputs in the space of the sensory RFs (i.e. on the skin or the retina) from the position of the eliciting stimuli in external space, either by changing hand posture or gaze direction of participants without moving their head (Macaluso & Maravita, 2010). Several behavioral (e.g. Kennett et al., 2002), electrophysiological (e.g. Eimer et al., 2001; Kennett et al., 2001; Macaluso, Driver, van Velzen, & Eimer, 2005) and neuroimaging studies (e.g. Macaluso et al., 2002) demonstrated that crossmodal visuo-tactile influence is rather dependent on the co-occurrence of both stimuli in external space rather than on the anatomical correspondence of the primary sensory projections in the cortex. Similarly for visual-nociceptive interactions, De Paepe et al. (2015) succeeded to demonstrate, by manipulating hand posture while keeping gaze constant, that visual stimuli affect the perception of nociceptive stimuli when both stimuli occur in the same external spatial position, irrespective of hand posture, suggesting that an initial somatotopic reference frame of the body space for the localization of nociceptive input is remapped into a spatiotopic reference frame, taking the relative position of body limbs in external space into account. Here, we extended these results, showing that, by using manipulation of gaze direction while keeping the position of the head constant, nociception, for its part, also influences visual perception based on their correspondence in external space. Combined with previous results showing that the way a nociceptive stimulus affects visuospatial processing is related to the spatial congruency between the hand on which nociceptive stimuli were applied and the visual stimuli, independently of the relative distance of both the stimulated hand and the visual stimuli from the body considered as a whole, i.e. the trunk (Filbrich, Alamia, Blandiaux, Burns, & Legrain, 2017a), the present results could suggest that visual stimuli can be remapped according to their proximity to specific body parts into a peripersonal representation of external space.

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