

Seeing or not Seeing Where Your Hands Are. The Influence of Visual Feedback About Hand Position on the Interaction Between Nociceptive and Visual Stimuli

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Abstract

Examining the mechanisms underlying crossmodal interaction between nociceptive and visual stimuli is crucial to understand how humans handle potential bodily threats in their environment. It has recently been shown that nociceptive stimuli can affect the perception of visual stimuli, provided that they occur close together in external space. The present study addresses the question whether these crossmodal interactions between nociceptive and visual stimuli are mediated by the *visually* perceived proximity between the visual stimuli and the limb on which nociceptive stimuli are applied, by manipulating the presence vs. absence of visual feedback about the position of the stimulated limb. Participants performed temporal order judgments on pairs of visual stimuli, shortly preceded by nociceptive stimuli, either applied on one hand or both hands simultaneously. The hands were placed near the visual stimuli and could either be seen directly, seen through a glass barrier, or hidden from sight with a wooden board. Unilateral nociceptive stimuli induced spatial biases to the advantage of visual stimuli presented near the stimulated hand, which were greater in the conditions in which the hands were seen than in the condition in which vision was prevented. Spatial biases were not modulated by the presence of the glass barrier, minimizing the possibility that the differential effect between the vision and no-vision conditions is solely due to the presence of the barrier between the hands and the visual stimuli. These findings highlight the importance of visual feedback for determining spatial mapping between nociceptive and visual stimuli for crossmodal interaction.

Keywords

Multisensory interaction, nociception, vision, proprioception, peripersonal space, temporal order judgment

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1. Introduction

Perceiving and interacting with the environment around us requires an optimally integrated spatial representation of the body and its surrounding space. In cognitive neuroscience, such a representation of space is conceptualized by the notion of peripersonal frame of reference, a reference frame coordinating the processing and integration of somatic and non-somatic stimuli occurring near the body (see Serino, 2019 for a review). The existence of such peripersonal representations has been studied extensively these recent years, mainly focusing on the mechanisms underlying interactions between visual and tactile stimuli. A peripersonal reference frame for spatial processing of sensory events supposes indeed that perceiving or reacting to a somatic stimulus can potentially be affected by a non-somatic stimulus, and vice versa. In non-human primates, multiple studies indicate that such visuo-tactile interactions rely on the existence of multimodal neurons, i.e., neurons able to respond to stimuli of different sensory modalities, such as visual and tactile stimuli, mostly in the ventral parts of the premotor cortex (vPM) and the intraparietal sulcus (VIP). More specifically, these neurons associate somatosensory and visual receptive fields with the particularity that the visual receptive field is spatially anchored to the somatosensory receptive field, i.e., spatially limited to the part of space immediately adjacent to the body (Duhamel *et al.*, 1998; Fogassi *et al.*, 1992; Gentilucci *et al.*, 1983; Graziano *et al.*, 1994, 1997; Rizzolatti *et al.*, 1981a, b). In humans, the peripersonal frame of reference has been demonstrated by studying brain-damaged patients suffering from crossmodal extinction. These patients have difficulties in perceiving a tactile stimulus applied on the hand contralateral to the damaged cortical hemisphere when it is concomitantly presented with a visual stimulus on the ipsilesional side of space. Importantly, this effect of the visual stimulus on tactile perception is strongest when the visual stimulus is presented in the direct vicinity of the ipsilesional hand and much weaker when it is presented farther away (i.e., in extrapersonal space) or close to a non-homologous ipsilesional body part (e.g., di Pellegrino *et al.*, 1997; Farnè *et al.*, 2005; Làdavas *et al.*, 1998). Studies in healthy humans corroborate these findings, showing that perceiving and reacting to a stimulus of one sensory modality, i.e., either tactile or visual, is influenced by the occurrence of a stimulus of the other modality, and that such crossmodal interactions between touch and vision are modulated by the proximity between the two sensory inputs (Holmes and Spence, 2004; Serino, 2019). Furthermore, several neuroimaging and electrophysiological studies have been able to highlight possible neural correlates of such crossmodal interactions in humans, suggesting the importance of premotor and posterior parietal areas for peripersonal space perception, as already shown in

non-human primates (e.g., Bremmer *et al.*, 2001; Gentile *et al.*, 2011; Kennett *et al.*, 2001; Macaluso *et al.*, 2002; Sereno and Huang, 2006).

Whereas the existence and characteristics of the peripersonal reference frame have been extensively studied in the context of the interaction between tactile and proximal visual stimuli, such investigations have only recently been instigated in the context of nociception and pain (Legrain and Torta, 2015). Indeed, it has been hypothesized that the function of such peripersonal representations, besides optimizing the manipulation of innocuous objects, would also be to shape defensive actions against physically threatening and potentially noxious stimuli (Graziano and Cooke, 2006). Next to its interoceptive function of warning the brain about possible body damage by nociceptive stimuli, nociception also has an exteroceptive function of providing information on external stimuli that could have the potential to damage the body (Haggard *et al.*, 2013). A prompt and efficient reaction to nociceptive stimuli therefore requires an optimally integrated multisensory, i.e., peripersonal, representation of the body and its surrounding space, allowing crossmodal interactions with external stimuli, such as visual ones. Studying interactions between nociception and vision as well as the conditions under which they occur is also clinically relevant, since it has been shown that some specific chronic pain conditions can affect the patients' abilities to represent and perceive the visual space surrounding their body (Bultitude *et al.*, 2017; Filbrich *et al.*, 2017a). In addition, targeting these cognitive difficulties has been suggested as a potentially useful method to treat chronic pain (Torta *et al.*, 2016). Clarifying the role of a peripersonal frame of reference in localizing nociceptive stimuli is thus not only important to apprehend how nociception is integrated with other sensory information to build a full representation of physical threats, but also to deepen the understanding of the pathophysiology of chronic pain disorders.

The involvement of the peripersonal frame of reference in processing sensory inputs that specifically activate skin nociceptors has recently been demonstrated in humans. Using temporal order judgment (TOJ) tasks, during which participants discriminate the temporal order of two lateralized stimuli presented in rapid temporal succession, several studies indeed demonstrated that nociceptive stimuli can interact closely with proximal visual stimuli (De Paepe *et al.*, 2014, 2015, 2017; Filbrich *et al.*, 2017b, c, 2018; Vanderclausen *et al.*, 2017). Filbrich *et al.* (2017b), for instance, showed that visual TOJs are systematically biased by the presence of a unilateral nociceptive stimulus shortly preceding the visual target stimuli. More precisely, the non-informative nociceptive stimulus applied on a hand attracted attention to its location (i.e. induced a spatial bias) in order to facilitate the processing of the visual stimuli occurring on the same side of space as the limb to which the nociceptive stimulus was applied. Importantly, such an interaction between nociceptive

and visual stimuli was mainly dependent on the proximity of the visual stimuli to the hand on which nociceptive stimuli were applied, irrespective of the relative position of both the stimulated limb and of the visual stimulus with regard to the body considered as a whole, as well as of the direction of gaze (Filbrich *et al.*, 2017c, 2018; Vanderclausen *et al.*, 2017). While these latter studies demonstrated that nociceptive stimuli can affect the perception and processing of visual stimuli, the reverse has also been observed. De Paepe *et al.* (2014) showed that nociceptive TOJs can be affected by the presence of a shortly preceding lateralized visual stimulus, provided that the nociceptive and the visual stimuli are presented close together (De Paepe *et al.*, 2015, 2017). Additionally, proximal visual stimuli have been shown to facilitate motor responses to nociceptive stimuli (De Paepe *et al.*, 2016), as well as to influence their detection (Filbrich *et al.*, 2019).

The results of these latter studies suggest that nociceptive stimuli can be processed, similarly to touch, according to a peripersonal reference frame, allowing them to interact with visual stimuli when both the nociceptive and the visual stimuli occur close to each other in external space. What is currently not clear, however, is to what extent these crossmodal interactions between nociceptive and visual stimuli are mediated by the visually perceived proximity between the non-somatic stimuli and the limb on which the somatic stimuli are applied. In the context of visuo-tactile interactions, it has for example been shown that the responsiveness of the monkey's vPM multimodal neurons to visual stimuli presented near the stimulated body part can be reduced when the body part is hidden from view (Graziano, 1999). This indicates that seeing the stimulated body part seems to play a crucial role in determining the spatial proximity between touch and vision in peripersonal space. Similar observations have been made in humans, where the accuracy in determining the position of an immobile hand decreases in the absence of visual information about the hand (see discussion in Holmes, 2013), which could in turn lead to difficulties in perceiving the proximity between the somatic and the visual stimulus in the absence of vision. However, empirical studies in humans are not consistent in their conclusions regarding the role of visual feedback in visuo-tactile interactions, possibly related to the differences in the studied populations and experimental paradigms. Whereas some of these studies conclude that visual information plays a predominant role in such interactions, others show that strong crossmodal effects between touch and vision are still possible when vision is prevented (see Kennett *et al.*, 2002; Làdavas *et al.*, 2000; Macaluso *et al.*, 2002; Mattingley *et al.*, 1997; Pavani *et al.*, 2000).

In the present study, we investigated the role of visual feedback about hand position on the above-mentioned crossmodal influence of nociceptive stimuli on the perception of visual space (Filbrich *et al.*, 2017b, c, 2018; Vanderclausen *et al.*, 2017). This crossmodal influence between nociceptive and

visual stimuli could indeed rely on the seen position of the stimulated hand, and thus on its *visually* perceived proximity to the visual stimuli in external space (i.e., visual information about the hand), but also on other feedback, such as proprioceptive information, for example. More precisely, we tested the effects of lateralized nociceptive cues on visual TOJ while vision of the hands on which nociceptive stimuli were applied was prevented by a wooden board or not. If the crossmodal effects between nociception and vision strongly depend on the *visually* perceived proximity between the two stimuli, the nociceptive cues should not induce any, or at least significantly smaller, spatial biases in the perception of visual target stimuli in the condition in which the view of the participants' hands is prevented, as compared to the condition in which the hands are seen. On the contrary, if visuo-nociceptive interactions are not mainly driven by visual feedback, the nociceptive cues should have similar effects on visual perception whether the hands are seen or not. Furthermore, to exclude the possibility that any potential differential effect between the *vision* vs *no-vision* conditions could be due to the mere presence of the wooden board between the hands and the visual stimuli in the *no-vision* condition, rather than to the fact that the position of the hands can be seen or not, we also included a condition in which the hands could be seen through a glass barrier placed between the hands and the visual stimuli. Indeed, one could hypothesize that crossmodal visuo-nociceptive interactions could merely be influenced by whether or not the visual stimuli are physically reachable (see Farnè *et al.*, 2003; Kitagawa and Spence, 2005; and Marquardt *et al.*, 2015 for a related discussion in the context of touch). If this was the case, spatial biases in visual perception induced by the nociceptive stimuli should be different in the condition in which a glass is placed between the hands and the visual stimuli as compared to a condition in which the hands are seen directly.

2. Materials and Methods

2.1. Participants

Twenty-five volunteers participated in the study. The data of two participants were excluded from the analyses due to inconsistent performance during the task (see Sect. 2.5. Data Analyses). The mean age of the remaining 23 participants (15 women) was 23.68 years ($SD = \pm 3.19$ years, range 21–35 years). Exclusion criteria were non-corrected vision difficulties, any neurological, cardiac, psychiatric or chronic pain disorder, trauma of the upper limbs within the last six months preceding the experiment, regular use of psychotropic drugs and intake of analgesic drugs (e.g., NSAIDs and paracetamol) within the 12 hours preceding the experiment. According to the Flinders Handedness survey (Flanders) (Nicholls *et al.*, 2013), 22 participants were right-handed

and one was left-handed. The local ethics committee (Commission d’Ethique Biomédicale Hospitalo-Facultaire, Saint-Luc University Hospital and Université Catholique de Louvain) approved the experimental procedure, in agreement with the Declaration of Helsinki. All volunteers signed a consent form prior to the experiment and received financial compensation for their participation.

2.2. *Stimuli and Apparatus*

Nociceptive stimuli were delivered by means of intraepidermal electrical stimulation (IES) using two stainless steel concentric bipolar electrodes (Nihon Kohden, Tokyo, Japan; Inui *et al.*, 2006). Electrical current was generated using DS7a stimulators (Digitimer Ltd, Welwyn Garden, UK). The IES electrodes consisted of a needle cathode (length 0.1 mm, Ø 0.2 mm) surrounded by a cylindrical anode (Ø 1.4 mm). Electrodes were gently pressed against each hand’s dorsum in order to insert the electrode in the epidermis of the sensory territory of the superficial branch of the radial nerve. IES has been shown to selectively and specifically activate cutaneous nociceptors, without concomitant activation of A β -fiber mechanoreceptors (responsible for tactile sensations), provided that very low intensities of stimulation are used (Legrain and Mouraux, 2013; Mouraux *et al.*, 2010, 2013, 2014). To guarantee the selective activation of A δ -fiber nociceptors, IES were set at twice the absolute detection threshold using single 0.5-ms square-wave pulses (Mouraux *et al.*, 2010), determined by means of a staircase procedure (Churyukanov *et al.*, 2012). If necessary, intensity values were adapted to guarantee that stimulus intensities were perceived as equivalent for both hands, by slightly increasing or decreasing the intensity of one of the two stimuli, with 0.5 mA as a maximum value (Favril *et al.*, 2014). During the experiment, stimuli consisted of trains of three consecutive 0.5-ms pulses separated by 5-ms interpulse intervals (Mouraux *et al.*, 2013, 2014). Using these parameters, stimuli were perceived as pricking, a sensation typically associated to the activation of A δ -fiber nociceptors (Mouraux *et al.*, 2010). Stimuli were not necessarily perceived as painful.

Visual stimuli (5 ms duration) were presented by means of two white-light-emitting diodes (LED) with a 17-lm luminous flux, a 6.40-cd luminous intensity, and a 120° diffusion angle (GM5BW97330A, Sharp Corporation, Osaka, Japan). These LEDs were perceived as brief flashes. An additional yellow LED (min. 0.1-cd luminous intensity at 20 mA, 120° diffusion angle, Farnell element 14, Multicomp, Leeds, UK) was used as fixation point during the task. LEDs were powered by means of an electrical pulse stimulator (Master-8, A.M.P.I., Jerusalem, Israel).

2.3. Procedure

The experiment took place in a dimly illuminated room. The participants were seated on a chair, placed their hands palm-down on a table and rested their head on a chin-rest (placed ~ 10 cm from the trunk). Each participant performed the visual temporal order judgments (TOJ) under three different *visibility* conditions (Fig. 1). First, in the *full-vision* condition, two white LEDs were taped on the table, at ~ 40 cm from the trunk, with a distance of 40 cm between them. The yellow fixation LED was placed at ~ 75 cm from the trunk, equidistantly from the two white LEDs, in front of the body midline. Each hand was placed next to one white LED (i.e., the right hand next to the right LED and the left hand next to the left LED), with a distance of maximally 1 cm between the LED and the metacarpophalangeal joint of the index finger. Second, in the *no-vision* condition, vision of the hands was prevented by masking them with a wooden board placed on the table (81.5 cm long, 60.5 cm deep, 0.4 cm thick and 9.5 cm high). The white LEDs and the yellow fixation LED were taped on the wooden board at exactly the same distances from the trunk as in the *full-vision* condition. Participants' hands were placed palm-down on the table beneath the board, in the same position as in the *full-vision* condition, so that they were positioned just underneath the white LEDs taped on the board. Finally, the *vision through glass* condition was similar to the *no-vision* condition, with the exception that the wooden board was replaced by translucent acrylic glass (80 cm long, 60 cm deep, 0.4 cm thick and 9.5 cm high) to allow the hands beneath the LEDs to be seen. Hands and LEDs were positioned exactly as in the *no-vision* condition.

A trial started with the illumination of the yellow fixation LED and the participants were instructed to keep their gaze at this fixation point as long as it was switched on, i.e. during the whole trial. After 500 ms, a nociceptive stimulus was applied either on the left hand (unilateral stimulation), on the right hand (unilateral stimulation) or on both hands simultaneously (bilateral stimulation). Unilateral nociceptive stimulation was used as cue to attract spatial attention to one of the two hands, with the aim of selectively biasing the perception of the forthcoming visual stimuli. Bilateral nociceptive stimulation was used to orient attention unselectively to both hands, with the aim of controlling for task-unrelated lateralized biases in spatial attention. A bilateral cue condition was chosen instead of a no-cue condition in order to keep a similar level of general alertness between the unilateral and bilateral conditions (see Raz and Buhle, 2006). Two hundred milliseconds after the administration of the nociceptive stimulus/i, a pair of visual stimuli was presented, separated by one out of 20 possible time intervals (SOAs, for *stimulus onset asynchronies*): ± 200 , ± 145 , ± 90 , ± 75 , ± 60 , ± 45 , ± 30 , ± 15 , ± 10 and ± 5 ms (negative values indicate that the left LED was illuminated first, positive values indicate

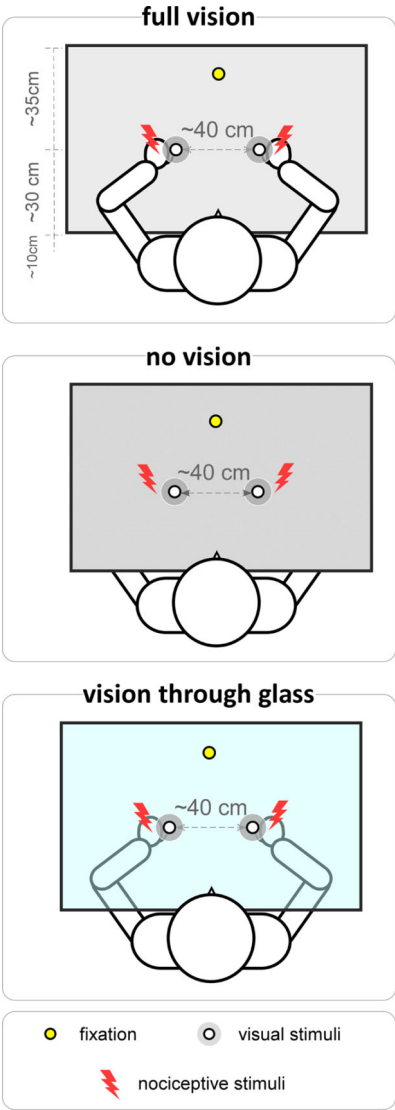


Figure 1. Design of the experiment. Participants performed temporal order judgments (TOJ) on pairs of visual stimuli (target LEDs, illustrated by the white circles with a slight grey halo), preceded by nociceptive stimulations (illustrated by the red flashes) applied either unilaterally, i.e., on one of the hands, or bilaterally, i.e., on both hands simultaneously. The participants' hands were always placed in the same position on the table, but depending on the condition, they were either visible (*full-vision* condition), occluded from sight (*no-vision* condition), or visible through acrylic glass (*vision through glass* condition). In the *full-vision* condition, the LEDs were fixed on the table, next to the hands, whereas in the *no-vision* and *vision through glass* conditions the LEDs were fixed on the board that was placed over the hands. A centrally-placed yellow LED (represented by the yellow circle) served as fixation point. This figure depicts the bilateral cues condition.

that the right one was illuminated first). At each trial, participants were asked to either judge which of the two visual stimuli they perceived as having occurred first, or, depending on the block, perceived as having occurred second, by verbally answering 'left' or 'right'. These two different response modalities were used to minimize potential response biases (see Filbrich *et al.*, 2016; Shore *et al.*, 2001; Spence and Parise, 2010 for a discussion). Responses were unspeeded, and no feedback was given regarding their performance. Once the experimenter encoded the participant's response (by pressing a key of the remote control computer), the yellow fixation LED turned off and the next trial started 2000 ms later. After each block, participants qualified the sensations on their hands and rated the perceived intensity of the nociceptive stimuli on a numerical rating scale (NRS) from 0 (= no sensation) to 10 (= very intense sensation) in order to ensure that the stimuli were still perceived as pinprick sensations of equal intensity between the two hands. If necessary, intensities could be adapted or the electrodes displaced and the assessment of the threshold restarted (see Favril *et al.*, 2014 for details).

Before starting the experiment, participants completed a training phase of two blocks to get familiarized with the procedure. The first block was composed of 10 trials in which participants were asked which stimulus they perceived as having occurred first. In a second block of 10 trials, they responded which stimulus they perceived as having occurred second. Trials of the training phase were performed using the same visibility condition as the one used in the first block of the experimental phase. During this training, the participants' performance was not recorded. In the experimental part, participants were presented with six experimental blocks of 60 trials each, with two blocks per visibility condition. The order of the three visibility conditions was counterbalanced between the participants, with one block performed for each response mode (i.e., 'which is first?' vs 'which is second?', randomized for each participant). During each block, visual stimuli were preceded by a unilateral left-sided nociceptive stimulus in 20 trials, by a unilateral right-sided nociceptive stimulus in another 20 trials, and by bilateral nociceptive stimuli in the remaining 20 trials, randomly and equiprobably intermixed. In summary, regardless of the response mode, a total of 120 trials for each visibility condition was presented, with 40 trials of each cueing condition within each visibility condition. For each block, the SOA between the two visual stimuli presented at each trial was determined online based on the adaptive PSI procedure, considering the participant's performance on all previous trials within the specific cue condition (Filbrich *et al.*, 2017b, c; Kontsevich and Tyler, 1999). Every two blocks, the wooden or acrylic glass boards were placed or removed, depending on the visibility condition. Each block lasted approximately five minutes and the entire experiment, including instructions and threshold measurements, lasted about one hour.

2.4. Measures

The maximal intensity of the nociceptive stimuli, that is, the maximal intensity of the electrical current used during the experiment was measured separately for each hand in milliampere (mA). For each participant, ratings of the subjective perception of stimulus intensity, as measured with the NRS (from 0 to 10), were averaged across the blocks for each hand separately.

To assess the performance of the participants in the TOJ task, two measures were used: the point of subjective simultaneity (PSS) and the slope. We estimated these measures as the α and β parameters of a logistic function, i.e., $f(x) = 1/[1 + \exp[-\beta(x - \alpha)]]$, respectively. Regarding our hypothesis, the main parameter of interest is α , defining the threshold of the logistic function, which 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 as occurring simultaneously (Spence *et al.*, 2001). In the present study, the PSS was used as a measure of spatial bias, indicating whether the judgments on the visual targets were shifted to the advantage of visual stimuli on one specific side of space. The β parameter defines the slope of the logistic function, which describes the noisiness of the results and can be related to the precision of participants' responses during the experiment (Kingdom and Prins, 2010). Since the adaptive PSI method was used (Kontsevich and Tyler, 1999), the logistic function and its parameters were estimated at each trial. This method is based on an algorithm that adopts a Bayesian framework, with the ultimate goal of estimating the parameters of interest without probing extensively all the SOAs (see Filbrich *et al.*, 2017b for a more detailed description of the PSI method in TOJ experiments).

To get a single measure of the performance during the unilateral cue condition for each participant and each experimental condition, the average of the PSS values for the left-sided cue condition and the values for the right-sided cue condition (multiplied by -1 for the PSS for the right-sided cue condition) was calculated. For the bilateral cue condition, the proportion of trials in which the left visual stimulus was reported as appearing first was plotted as a function of SOA. For the unilateral cue condition, the proportion of trials in which the visual stimulus presented in the cued side of space was reported as appearing first was plotted as a function of SOA.

2.5. Data Analyses

Participants' data were excluded from statistical analyses if the threshold and slope of the psychometric function could not be reliably estimated during the 20 trials of one or several cue conditions (i.e., their respective estimates did not

converge on a stable value on the last trials), indicating that their performance was too inconsistent and below chance level.

Analyses were conducted using SPSS Statistics 23 (IBM Corp., Armonk, NY, USA). First, to verify that the two hands were stimulated with similar intensities, the mean scores of the maximal intensity of the nociceptive stimuli were compared between the two hands using a *t*-test for paired samples. Because the self-reported perception of stimulus intensity can be considered as an ordinal variable, the NRS values were compared between the two hands using a non-parametric Wilcoxon signed-rank test.

Before analyzing the TOJ data, data from the two response modalities ('*which is first?*' vs '*which is second?*') were averaged for each condition to reduce the potential contribution of responses biases. To highlight potential shifts in visual TOJs to one side of space, the mean PSS value of each condition was compared to 0 with a one-sample *t*-test. Furthermore, to analyze differences between the conditions, we performed an analysis of variance (ANOVA) for repeated measures on PSS and slope measures, respectively, with *visibility* (*full vision* vs *no vision* vs *vision through glass*) and *cue* (*unilateral* vs *bilateral*) as within-participant factors. If necessary, Greenhouse–Geisser corrections of degrees of freedom were applied. A-priori contrast analyses were used to specifically address our hypotheses. Because we hypothesized that the shifts in visual TOJs induced by the unilateral nociceptive cues could be differently affected according to the visibility condition, three contrasts analyses were planned to compare the three visibility conditions for the unilateral cue condition with each other. Significance level was set at $p \leq 0.05$. Effect sizes were measured using Cohen's *d* for *t*-tests and partial η^2 for ANOVAs.

3. Results

3.1. Intensity Values

The *t*-test revealed no significant difference [$t(22) = 0.46$, $p = 0.650$, $d = 0.09$] regarding the maximal intensity of the nociceptive stimuli between the two hands ($M = 0.3 \pm 0.1$ mA for the left hand and $M = 0.29 \pm 0.09$ mA for the right hand). These values are in the range of intensities that have been shown to selectively activate A δ nociceptors (Mouraux *et al.*, 2010, 2013, 2014). Self-reported NRS values were also not significantly different between the left ($Mdn = 3.33$) and the right hand ($Mdn = 3.33$) ($Z = -0.71$, $p = 0.474$). These results indicate that similar intensities of electrical current were used for the two hands, and that nociceptive stimuli were judged as equally intense between the two hands.

3.2. Temporal Order Judgments

The one-sample t -test revealed that PSS values of the unilateral cue condition were significantly different from 0 for the three *visibility* conditions [*full vision*: $t(22) = 7.68$, $p < 0.001$, $d = 1.60$, $M = 20.83$, $SD = 13$; *no vision*: $t(22) = 7.06$, $p < 0.001$, $d = 1.47$, $M = 16.16$, $SD = 10.97$; *vision through glass*: $t(22) = 8.44$, $p < 0.001$, $d = 1.76$, $M = 21.5$, $SD = 12.22$]. Conversely, these differences were not significant in the bilateral condition [*full vision*: $t(22) = -0.10$, $p = 0.919$, $d = -0.02$; *no vision*: $t(22) = 0.68$, $p = 0.505$, $d = 0.14$; *vision through glass*: $t(22) = -0.54$, $p = 0.593$, $d = -0.11$]. This indicates that in the unilateral cue conditions, visual stimuli presented on the side of space opposite to the nociceptive cue had to be presented several milliseconds before stimuli presented on the cued side of space to have the chance to be judged as occurring simultaneously. In other words, PSS values were significantly biased to the advantage of the visual stimuli presented on the side of space corresponding to the hand to which the nociceptive stimulus was applied. Conversely, no significant bias to the advantage of one of the two sides was observed in the bilateral cue conditions (see Figs 2 and 3).

The ANOVA of the PSS values did not show a significant main effect of the factor *visibility* [$F(2, 22) = 0.13$, $p = 0.877$, $\eta_p^2 < 0.01$]. On the contrary, there was a significant main effect of the factor *cue* [$F(1, 22) = 39.78$, $p < 0.001$, $\eta_p^2 = 0.64$], which also significantly interacted with the factor *visibility* [$F(2, 22) = 4.16$, $p = 0.022$, $\eta_p^2 = 0.16$]. This suggests that while the visibility of the hands did not affect the PSS in the bilateral cue condition [$F(2, 22) = 1.07$, $p = 0.351$, $\eta_p^2 = 0.05$], it had a significant impact on the PSS in the unilateral cue condition [$F(2, 22) = 4.76$, $p = 0.013$, $\eta_p^2 = 0.18$] (Fig. 2). In agreement with our hypotheses, a-priori contrast analyses revealed that, as compared to the *no-vision* condition, the PSS was larger in the *full-vision* [$t(22) = 2.24$, $p = 0.035$, $d = 0.47$] and in the *vision through glass* conditions [$t(22) = -2.76$, $p = 0.011$, $d = 0.58$]. There was no significant difference between the *full-vision* and *vision through glass* conditions [$t(22) = -0.41$, $p = 0.683$, $d = 0.09$]. This suggests that the bias induced by the unilateral cues was greater when the hands were seen, as compared to when their vision was prevented (see Fig. 2).

Regarding the slope, the ANOVA revealed no significant main effect, neither for the factor *visibility* [$F(2, 22) = 2.27$, $p = 0.115$, $\eta_p^2 = 0.09$] nor for the factor *cue* [$F(1, 22) = 0.04$, $p = 0.837$, $\eta_p^2 < 0.01$]. There was, however, a significant interaction between these two factors [$F(2, 22) = 4.38$, $p = 0.013$, $\eta_p^2 = 0.18$], suggesting that the *visibility* factor did not significantly impact the slope of the *bilateral cue* condition [$F(2, 22) = 1.53$, $p = 0.228$, $\eta_p^2 = 0.06$], but did affect the slope of the *unilateral cue* condition [$F(2, 22) = 3.40$, $p = 0.042$, $\eta_p^2 = 0.13$]. Indeed, the slope value was greater

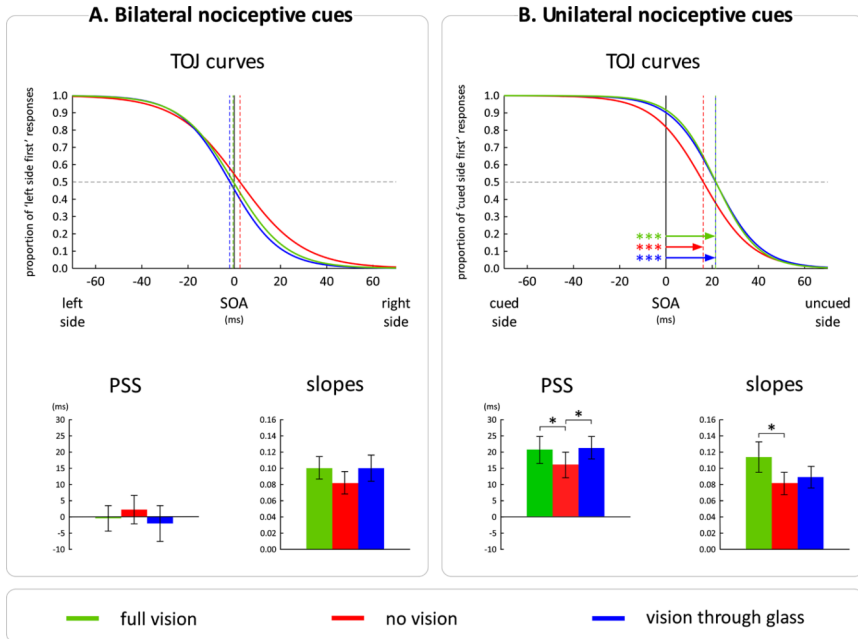


Figure 2. Results of the experiment. The figure illustrates the averaged results of the 23 participants. Data from left-sided nociceptive cue conditions and right-sided nociceptive cue conditions were averaged into a unilateral cue condition. The upper part depicts the fitted logistic functions for (A) the bilateral cue condition and (B) the unilateral cue condition. For the bilateral cue condition (A), the x -axis represents different hypothetical stimulus onset asynchronies (SOAs) between the two visual stimuli: negative SOA values indicate that the visual stimulus occurring in the left side of space was presented first, while positive values indicate that the visual stimulus occurring in the right side of space was presented first. The y -axis represents the proportion of trials in which the participants perceived the stimulus presented in the left side of space as occurring first. For the unilateral cue condition (B), the x -axis represents different hypothetical stimulus-onset asynchronies (SOAs) between the two visual stimuli: negative values indicate that the visual stimulus occurring in the cued side of space was presented first, while positive values indicate that the visual stimulus occurring in the uncued side of space was presented first. The y -axis represents the proportion of trials in which the participants perceived the visual stimulus presented in the cued side of space as occurring first. In both (A) and (B), red curves represent the *no-vision* condition, with the corresponding PSS values indicated by the red vertical dashed lines. Blue curves represent the *visible through glass* condition, with the corresponding PSS values indicated by the blue vertical dashed lines. Green curves represent the *full-vision* condition, with the corresponding PSS values indicated by the green vertical dashed lines. The arrows in (B) indicate PSS values significantly different from zero. The curves in the unilateral cue condition (B) are significantly shifted to the uncued side of space, indicating that visual stimuli presented in the uncued side of space had to be presented several ms before the stimuli presented in the cued side of space to have the chance to be perceived as occurring first equally often. The lower part illustrates the mean PSS and slope values, for both bilateral (A) and unilateral (B) cue conditions. Significant differences are indicated with asterisks (* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$). Error bars represent the 95% confidence intervals adapted according to the method of Cousineau (2005).

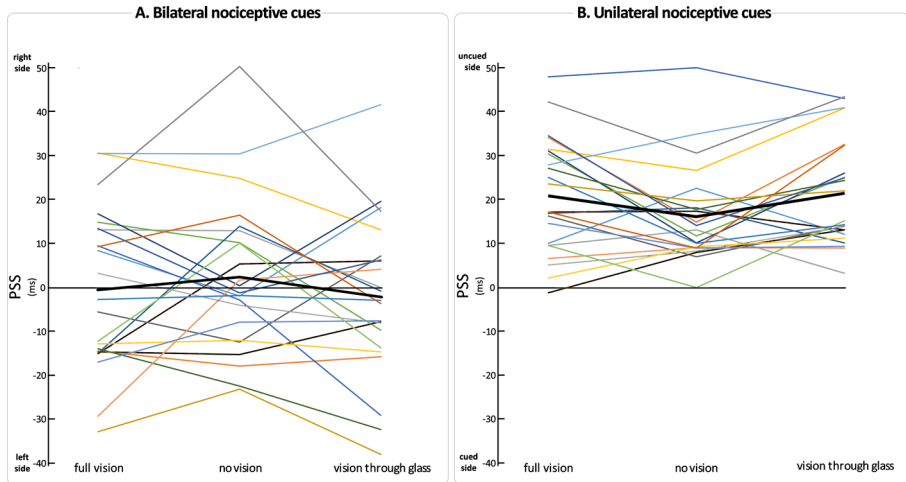


Figure 3. Individual PSS values. The left graphic illustrates the PSS values for the bilateral nociceptive cue condition (A), and the right graphic the PSS values for the unilateral nociceptive cue condition (B). Within each graphic, values are represented for each visibility condition (full vision vs no vision vs vision through glass). Each colored line represents one of the 23 participants, while the black line represents the group average.

in the *full-vision* condition [$M = 0.11$, $SD = 0.06$] as compared to the *no-vision* condition [$M = 0.08$, $SD = 0.04$; $t(22) = 2.256$, $p = 0.034$, $d = 0.47$]. The other paired comparisons did not reveal any significant differences (slope value of the *vision through glass* condition: $M = 0.09$, $SD = 0.05$; *full-vision* vs *vision through glass* comparison: $t(22) = 1.88$, $p = 0.074$, $d = 0.39$; *vision through glass* vs *no-vision* comparison: $t(22) = -0.67$, $p = 0.507$, $d = -0.14$). This suggests that, when a nociceptive stimulus was applied on one single hand before the presentation of the visual stimuli, preventing vision of the hands made the participants' judgments more noisy, i.e., variable, as compared to the condition in which the hands could be seen directly.

4. Discussion

The aim of the experiment was to test whether the crossmodal influence of nociception on visual perception, which relies on the proximity of both types of stimuli in external space (Filbrich *et al.*, 2017b, c, 2018; Vanderclausen *et al.*, 2017), is mediated by visual feedback about the position of the stimulated limb with regard to the visual stimuli. More precisely, we tested if spatial biases in visual TOJ, induced by nociceptive cues applied on the hands positioned next to visual targets, are affected when the visually perceived proximity between the hands and the visual stimuli is disrupted. Participants judged the temporal order of pairs of visual stimuli which were preceded by task-unrelated

nociceptive stimuli applied either unilaterally, i.e. on one of the hands, or bilaterally, i.e., on both hands simultaneously. The hands were always placed close to the visual stimuli. While bilateral nociceptive stimuli were used as control condition, unilateral nociceptive stimuli were used as cues to attract spatial attention to one side of space and thus to induce crossmodal spatial biases. According to the theory of prior entry (Titchener, 1908), stimuli on which we focus our attention are perceived earlier than unattended ones. In the present study, the time interval between the two visual stimuli that is necessary for the two to be perceived as occurring at the same time (i.e., the PSS) can thus be used to index the presence of spatial biases.

The results replicated previous findings, showing that the presence of a unilateral nociceptive cue can induce spatial biases in visual perception, with TOJs prioritizing the visual stimulus presented on the same side of space as the hand on which the single nociceptive stimulus was applied (Filbrich *et al.*, 2017b, c, 2018; Vanderclausen *et al.*, 2017). Importantly, such significant spatial biases were observed in all three visibility conditions, whether the proximity between the nociceptive cues and visual targets was visually perceived or not. Nevertheless, comparisons between these three visibility conditions revealed that spatial biases were significantly greater in the two conditions in which the hands could be seen, as compared to the condition in which seeing the hands was prevented by the wooden board. This finding could potentially suggest that the visual feedback about the hands' position plays a predominant role in determining spatial congruency between nociceptive and visual stimuli. That crossmodal interactions between somatic and non-somatic stimuli could mainly be due to the visually perceived proximity between the two types of stimuli has indeed previously been suggested by studies in brain-damaged patients. These studies directly compared the influence of seeing vs not seeing the hands on the strength of the crossmodal extinction of tactile contralesional stimuli by visual stimuli presented near the ipsilesional hand (Làdavias *et al.*, 2000). Strikingly, they observed strong crossmodal effects when the hands were visible, but only mild effects when seeing the hands was prevented. Although the effect was still present when the hands were covered, its magnitude was similar to the one of the crossmodal effect induced by a visual stimulus presented farther away from the hand (i.e., in extrapersonal space). This latter result potentially suggests that without visual feedback, and solely based on proprioceptive information, the relative location of the stimulated limb with regard to external stimuli could be difficult to determine, thus leading to difficulties in determining whether a visual stimulus is presented near or far from the limb. The importance of seeing the stimulated hand next to the visual stimuli for visuo-tactile interactions has also been corroborated in healthy humans by Maravita *et al.* (2002). They showed that visual stimuli that are seen close to the reflection of the participants' hands in a distant mirror have a greater

impact on the perception of tactile stimuli applied on the hands than visual stimuli that are presented at an equivalent distance but without sight of the hands.

Nevertheless, although we showed a significant difference between the conditions preserving vision of the hands and the condition preventing it, our results and those of the above-mentioned studies do not actually allow us to conclude that the proximity effect in interactions between nociceptive and visual stimuli mainly relies on visual feedback, or that proprioceptive feedback seems less important. First of all, we still observed strong spatial biases in visual TOJs induced by the nociceptive cues in the condition in which seeing the hands was prevented, suggesting that proprioceptive input about the position of the stimulated hands is used to determine the spatial proximity between the nociceptive and visual stimuli. Although we did not directly compare the effects of visual stimuli presented at different distances from the stimulated hand, the present biases in the *no-vision* condition appear much stronger than the effects found with far visual stimuli in previous studies (see Filbrich *et al.*, 2017c) and seem thus different from the above-mentioned results of Làdavas *et al.* (2000). In addition, previous investigations in the context of visuo-tactile interactions have been able to demonstrate strong crossmodal effects even though vision of the hands was prevented. For instance, Kennett *et al.* (2002) showed in healthy participants that tactile distractor stimuli can influence visual performance (and vice versa) in a crossmodal congruency task when the stimulated hand is not seen. Similarly, Mattingley *et al.* (1997) observed in brain-damaged patients suffering from crossmodal extinction that a tactile stimulus applied on the unseen ipsilesional hand can extinguish the perception of a simultaneous contralesional visual stimulus (and vice versa). Furthermore, Macaluso *et al.* (2002) showed that tactile stimuli can boost the cortical responses to visual stimuli in the visual cortex when both stimuli are spatially aligned in external space, regardless of whether the stimulated hand is seen or not. Notably, there is even one study that obtained larger crossmodal effects between touch and vision in the crossmodal congruency task when the hands were hidden from sight than when they were visible (Kitagawa and Spence, 2005).

Another point that prevents us from concluding on a predominant role of visual feedback in the observed crossmodal interactions relies on the fact that we did not test a condition in which only visual information about the proximity between nociceptive and visual stimuli was provided, i.e., without any proprioceptive feedback. Indeed, it could be that the combination of both visual and proprioceptive feedback about limb position optimizes interaction effects between somatic and extra-somatic stimuli, as compared to a situation in which only one of these feedbacks is available. While it seems certainly difficult to completely suppress any proprioceptive feedback, and thus to properly

disentangle the respective roles of vision and proprioception in determining spatial proximity between the body and external objects, proprioceptive feedback can actually be manipulated by experimentally induced illusions. For instance, Pavani *et al.* (2000) showed significantly larger effects of proximal visual distractors on tactile perception when a fake hand was placed in a realistic position above the hidden stimulated real hand (and thus close to the visual stimuli), as compared to conditions in which the real hand was just hidden. Similarly, Gallace and Spence (2005) showed that simply raising the visual illusion of a changed hand posture, by varying the distance between a hand and its mirror-reflected image, affected participants' performance during tactile TOJ, while the actual hand position (i.e., proprioception) remained unchanged. This suggests that under specific circumstances, e.g., when vision and proprioception are mismatching, visual feedback about limb position can overrule proprioceptive feedback.

In addition to determining the role of the visual feedback about hand position in the interaction between nociceptive and visual stimuli, the present study also addressed the question whether such interactions between somatic and non-somatic stimuli could be mediated by the expectancy of imminent contact with the external object. This question is of particular relevance when stimuli activating the nociceptive system are involved, specifically if an external object (i.e., visual stimulus) is presented close to a hand that is already stimulated with a nociceptive stimulus, as in the present study. Since one of the main functions of the peripersonal representation would be to defend the body against potentially noxious stimuli, one could indeed argue that if the body is protected from any contact with external objects that could potentially threaten its physical integrity, crossmodal interactions between the somatic and non-somatic systems would be disrupted. In the present study it could indeed be possible that the crossmodal effect between nociceptive and visual stimuli in the *no-vision* condition was smaller than in the vision conditions because the potential contact between the visual stimuli and the hand was prevented, rather than because hand position was not seen. To take into account this possibility, the condition with a translucent glass barrier was included, which provided the participants with visual feedback about the spatial proximity between the stimulated hand and the visual stimulus, while rendering any potential physical contact between the nociceptive and visual stimuli impossible. Our results show that the spatial bias induced by the nociceptive stimuli in the condition in which the hands could be seen through the glass was not significantly different from the one observed in the condition in which the hands could be seen directly. In other words, similar crossmodal effects were observed whether a potential contact between nociceptive cues and visual targets was possible or not. Similar results have been previously shown in the context of visuo-tactile interactions. Farnè *et al.* (2003) demonstrated in brain-damaged

patients that the perceptual extinction of tactile stimuli by near visual stimuli does not change with the presence of a transparent barrier between the two stimuli. Likewise, in healthy participants, Kitagawa and Spence (2005) did not report any differential effect of seeing the hands through a transparent occluder on visuo-tactile interactions in the crossmodal congruency task. It seems thus that the multisensory processing in the space surrounding the stimulated body part is not mediated by the expectancy of contact with external objects, even in the context of noxious objects, and that interaction between nociceptive and nearby non-somatic stimuli occurs automatically, whether they are physically separated or not. This has been interpreted as indicating that such crossmodal interactions can occur in a bottom-up fashion without being influenced by higher-order top-down processes, potentially related to their importance for triggering fast and appropriate motor reactions in peripersonal space (Farnè *et al.*, 2003).

However, one has to note that in the present study, contrary to Farnè *et al.* (2003), contact between the visual stimuli and the hands could not really have been expected by the participants, since the visual stimuli consisted in static flashing LEDs. To disentangle the role of visual feedback about hand position from the expectancy of being touched more thoroughly, it would be interesting to use visual stimuli that can induce the expectancy of an impending physical contact with the body (see also Kitagawa and Spence, 2005). This could boost the relevance of a transparent barrier between the nociceptive stimuli and near visual stimuli, and make any interaction between the two stimuli more likely to be mediated by its presence.

In conclusion, the present results suggest that visual feedback about the position of the limb on which nociceptive stimuli are applied plays an important role in establishing spatial alignment between nociceptive and visual stimuli in external space, whether both types of stimuli are physically separated or not. What still needs to be determined is whether such visual feedback can be disentangled from proprioceptive feedback, and if spatial mapping between somatic and non-somatic stimuli predominantly relies on one of these feedbacks.

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