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RESEARCH ARTICLE

Orienting attention in visual space by nociceptive stimuli: investigation with a temporal order judgment task based on the adaptive PSI method

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Abstract Despite their high relevance for defending the integrity of the body, crossmodal links between nociception, the neural system specifically coding potentially painful information, and vision are still poorly studied, especially the effects of nociception on visual perception. This study investigated if, and in which time window, a nociceptive stimulus can attract attention to its location on the body, independently of voluntary control, to facilitate the processing of visual stimuli occurring in the same side of space as the limb on which the visual stimulus was applied. In a temporal order judgment task based on an adaptive procedure, participants judged which of two visual stimuli, one presented next to either hand in either side of space, had been perceived first. Each pair of visual stimuli was preceded (by 200, 400, or 600 ms) by a nociceptive stimulus applied either unilaterally on one single hand, or bilaterally, on both hands simultaneously. Results show that, as compared to the bilateral condition, participants' judgments were biased to the advantage of the visual stimuli that occurred in the same side of space as the hand on which a unilateral, nociceptive stimulus was applied. This effect was present in a time window ranging from 200 to 600 ms, but importantly, biases increased with decreasing time interval. These results suggest that nociceptive stimuli can affect the perceptual processing of spatially congruent visual inputs.

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Introduction

Pain is an unpleasant sensation usually evoked by the activation of nociceptors. Nociceptors are sensory receptors characterized by a high activation threshold, that is, by the ability to respond to high intensity and potentially harmful stimuli. The functional role of the nociceptive system is to warn the brain about possible body damage and to adapt behavior to possibly damaging stimuli to protect the integrity of the body. To this aim, the brain needs to locate which part of the body is potentially being harmed, an ability that depends partly on spatially organized projections of the receptor fields to specific spatially segregated groups of neurons in the cortex (Kenshalo and Isensee 1983). This mapping mechanism, based on an anatomical representation of the body surface, is however not sufficient. Indeed, responding adequately to a potential threat requires also to perceive the posture of the body (where is the threatened limb?) and to locate, for instance visually, the cause of the damage in external space (where is the threatening stimulus?) (Legrain et al. 2011). In other words, by integrating the relative position of the body limbs in external space, and by coordinating the representation of the body space with that of external space, the brain should be able, based on the perception of the location of a nociceptive and potentially painful stimulus, to orient attention selectively to the location of the external, e.g., visual, stimuli in order to prioritize their processing (Legrain and Torta 2015). Surprisingly, up to now, most of the research studying

crossmodal attention between nociceptive/painful[1] and external (auditory or visual) stimuli investigated the reverse link, i.e., how auditory or visual stimuli can attract attention to a particular spatial location and impact the processing and the perception of the intensity of a nociceptive/painful stimulus applied on the limb adjacent to this spatial location (e.g. Bushnell et al. 1985; Honoré et al. 1995; Dowman 2004; Van Ryckeghem et al. 2011; Van Damme and Legrain 2012). Most of these studies used cueing paradigms in which participants had to react to and/or to rate the intensity of a nociceptive/painful stimulus preceded by a visual stimulus at a congruent vs. incongruent spatial position. For instance, De Paepe et al. (2014, 2015), using temporal order judgement (TOJ) tasks (see below), have shown that the perception of a nociceptive stimulus applied on one limb was facilitated when it was preceded shortly by a visual stimulus presented in the proximity of the stimulated limb.

It is certainly interesting to understand how the reaction to a nociceptive stimulus and the pain elicited by such a stimulus can be modulated by the visual perception of an external object that might have an impending impact on the body. However, it seems even more ecologically relevant to understand how the perception of a nociceptive stimulus on the body can attract attention to the space surrounding the affected limb to prioritize the visual perception of stimuli occurring around that limb. To our knowledge, this question was only investigated by two studies. Van Damme et al. (2007) instructed their participants to react as fast as possible to visual stimuli presented at two possible locations, corresponding to each side of space, at the proximity of the wrist of each hand. They show that reactions to these visual stimuli were speeded-up when a painful stimulus preceded the occurrence of the visual stimulus by 200 ms, while being applied on the wrist of the hand spatially congruent with the visual stimulus, as compared to a painful stimulus applied to the opposite hand. However, these authors used transcutaneous electrical current induced by bipolar electrodes as painful stimuli, a stimulation that is known to activate all underlying somatosensory fibers, including large-diameter myelinated Aβ nerve fibers responsible for tactile sensation. Therefore, attentional capture induced by these painful stimuli was triggered by the fastest and first somatosensory inputs that reached the cortex, that is, the inputs conveyed by non-nociceptive Aβ fibers which are characterized by a faster velocity conduction than the slow conducting finely myelinated nociceptive Aδ and unmyelinated nociceptive C fibers (Kandel et al. 2013). In other words, the attentional effects observed in the study of Van Damme et al. (2007) were not related to the nociceptive specificity and the painfulness of the somatosensory stimuli. Using a slightly modified paradigm, Favril et al. (2014) obtained similar results, but with intra-epidermal electrical stimulation (IES) delivered at low intensities, a technique that has been shown to be more selective in activating nociceptive Aδ fibers (Inui et al. 2002, 2006; Mouraux et al. 2010). However, since in that study, the position of the visual target was highly predictable for the participants, it is difficult to disentangle whether the effects on visual processing were driven by the motivation of the participants to allocate attention to one side of space, or by the capture of attention triggered by the nociceptive stimulus itself to its own location.

The first objective of the present study was to show how a somatosensory stimulus applied to a particular body limb and specifically coded and transmitted by the nociceptive system, can attract attention to its location, independently of voluntarily control, to facilitate the processing of visual stimuli occurring in the same side of space as the limb on which the nociceptive stimulus is applied.

To this aim, we used a TOJ task during which participants were instructed to discriminate the temporal order of two stimuli presented in rapid temporal succession. As compared to classic detection and reaction tasks, TOJ tasks offer the advantage to be unspeeded and can thus highlight the effects of experimental manipulations on changes in the perceptual processing of a target stimulus without the confound of faster response selection and/or execution (Spence et al. 2004; Zampini et al. 2007). These tasks are regularly used to study crossmodal links in spatial attention between different sensory modalities (see for example Spence et al. 2001; De Paepe et al. 2014, 2015). Attentional effects observed during TOJ are interpreted in light of the theory of prior-entry (Titchener 1908), according to which the perception of attended stimuli is speeded-up as compared to unattended ones. As a consequence, an unattended stimulus has then to be presented before the attended stimulus to be perceived as occurring simultaneously. The stimulus onset asynchrony (SOA) at which the two stimuli are perceived as simultaneous has been defined as the point of subjective simultaneity (PSS) (for a review, see Spence and Parise 2010). In prior-entry-related TOJ tasks, shifts in the PSS are used to highlight changes in the perceptual sensory processing of target stimuli due to attentional manipulations such as attending to a particular location induced by spatial cueing. In the present study, we asked the participants to perform TOJs on pairs of lateralized visual stimuli, one stimulus presented close to either hand, while measuring the effects on the PSS induced by a nociceptive stimulus applied on one of the hands shortly before the pair of

[1] The term "nociceptive" is used to describe stimuli that selectively activate nociceptors, while the term "painful" is used to describe stimuli that are explicitly perceived as pain by the participant, regardless of the selectivity of the eliciting stimuli.

visual stimuli. We predicted a shift of the PSS values to the advantage of the visual stimuli presented close to the stimulated hand, indexing that their processing was facilitated by the nociceptive stimulus applied in the congruent spatial location.

The second aim of our study was to implement a TOJ task based on an adaptive procedure to vary the different SOAs between the two stimuli on which the TOJs are made and to finally derive the PSS. Indeed, in most of the existing TOJ studies, the method of constant stimuli is used (see Spence and Parise 2010). With this method, a sample of SOAs is chosen a priori, and the SOAs are repeated several times during the experiment. The disadvantage of the method of constant stimuli is that testing can be time-consuming and tedious as many trials have to be presented for each SOA to reliably derive the parameters of interest (Kingdom and Prins 2010). As a consequence, the number of tested experimental conditions has often to be reduced. The modification of the TOJ task used in the present study is based on the adaptive PSI method (Kontsevich and Tyler 1999). The advantage of using the PSI method is that it allows to estimate the distributions of the parameters (e.g., the PSS) with a lower number of trials, which accelerates the testing procedure, thus reducing confounding effects usually associated with long tasks, such as task-independent attention shifts and fatigue. Furthermore, the tested SOAs are adapted to each participant's own performance, which is of great interest for avoiding floor or ceiling effects when, for example, comparing the performance of two distinct types of participant populations. Indeed, TOJ tasks are regularly used to test perceptual capacities in clinical populations in which sensory processing might be disturbed, as for example in chronic pain (see Moseley et al. 2009, 2012; Reid et al. 2016) or right-hemisphere damaged patients (see Eramudugolla et al. 2007; Sinnett et al. 2007; Roberts et al. 2012). However, in these clinical studies, selection of presented SOA levels seems often based on studies assessing the performance of healthy subjects and rarely on the patients' own performance (for exceptions see Rorden et al. 1997; Robertson et al. 1998). Using procedures specifically adapted to individual performances seems thus to be more indicated when the aim is to highlight potentially subtle differences between experimental conditions or between specific participant populations. Besides the more theoretical aim of demonstrating crossmodal influence of nociception on visual perception with a TOJ task, the present study served thus also to assess an adaptive method aimed to increase the efficiency of the testing procedure.

The final aim of the present study was to test the time window during which a somatosensory stimulus specifically conveyed by the nociceptive system can efficiently capture attention and positively impact the processing of another stimulus presented in its spatial surrounding. One issue in cueing paradigms is that involuntary stimulus-driven capture of attention is short-living, and, that there is, therefore, a critical time window during which the cueing stimulus can efficiently impact the processing of the forthcoming target stimulus (Posner and Cohen 1984). While this aspect was already investigated for the other sensory modalities (e.g., Spence et al. 2004), the optimal time window for a nociceptive cue is completely unknown. Such a critical time window is partly dependent on the velocity of the sensory transmission. Since the conduction velocity of Aδ fibers is relatively slow as compared to Aβ fibers (Campbell and LaMotte 1983), nociceptive-induced attentional effects cannot be directly predicted from studies having used non-nociceptive somatosensory stimuli as cues, but are expected at a longer latency. For instance, Kennett et al. (2001) found strong crossmodal attentional effects when a tactile cue preceded the visual target by 160 ms, and less efficient, but still significant effects by 310 ms. On the other hand, since no cortical response is expected from nociceptive intra-epidermal electrical stimulation before 100–150 ms (Inui et al. 2003; Mouraux et al. 2013, 2014), no attentional effect is, therefore, expected in such a time window. Here, we tested three time intervals: 200, 400, and 600 ms between the onset of the nociceptive cue and that of the first visual stimulus of the pair.

Methods

Participants

Sixteen participants volunteered to take part in the experiment. One participant was not able to finish the experiment because of an uncontrolled startle response to the electrocutaneous stimuli. The mean age of the remaining 15 participants (10 women) was 23.4 years (SD = 4.99, range: 18–35 years). Participants had normal or corrected-to-normal vision and did not report any neurological, psychiatric, cardiac or chronic pain problems, regular use of psychotropic drugs, as well as any traumatic injury of the upper limbs within the 6 months preceding the experiment. They reported having slept at least 6 h before the experiment and not having used any analgesic drugs (e.g., NSAIDs and paracetamol) within the 12 h preceding the experiment. All but one of the participants were right-handed according to the Flinders Handedness Survey (Flanders) (Nicholls et al. 2013). The experimental procedure was approved by the local ethic committee in agreement with the latest version of the Declaration of Helsinki, and all participants signed a consent form prior to the experimental session. Participants received financial compensation.

Stimuli and apparatus

Nociceptive stimuli were delivered at the hand dorsum by means of intra-epidermal electrical stimulation (IES) (DS7 Stimulator, Digitimer Ltd., UK) using stainless steel concentric bipolar electrodes (Nihon Kohden, Japan; Inui et al. 2006), which consisted of a needle cathode (length: 0.1 mm, Ø: 0.2 mm) surrounded by a cylindrical anode (Ø: 1.4 mm). By pressing gently against the participant's skin, the electrode was inserted in the epidermis of each hand dorsum in the sensory territory of the superficial branch of the radial nerve. To selectively activate skin nociceptors, the intensity of the electrical stimulation was individually adjusted to twice the absolute detection threshold with a maximum of 0.5 mA as restriction criteria (Mouraux et al. 2010). For each of the participants' hands, detection threshold to a single 0.5 ms square-wave pulse was determined using 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 (see Favril et al. 2014 for details). During the experiment, stimuli consisted of trains of three consecutive pulses separated by a 5 ms interpulse interval (Mouraux et al. 2013, 2014). The participants described the IES sensation as pricking but not necessarily unpleasant. Using such a procedure, IES was shown to selectively activate Aδ nociceptors without co-activation of Aβ mechanoreceptors (Mouraux et al. 2010, 2013).

Visual stimuli 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° visual angle (GM5BW97330A, Sharp Corporation, Japan). They were perceived as brief flashes. To ensure the visibility of the LEDs, participants were asked to report the position of the flashing LED (i.e., the left or the right one). A third yellow LED (min. 0.7 cd luminous intensity at 20 mA, 120° viewing angle) was used as fixation point during the task (Multicomp, Farnell element14, UK).

Procedure

Participants were sitting in a dimly-illuminated testing room with their arms positioned on a table and their palms down. Their heads were stabilized with a chin-rest placed approximately 10 cm from the trunk, to minimize head movement. The two white LEDs were fixed on the table, approximately 40 cm away from the trunk and with a distance of 40 cm between them. Each participant's hand was placed next to one of the two LEDs, with a maximum distance of 1 cm between the LED and the joint between the metacarpal and the proximal phalange of the index finger. The yellow fixation LED was placed equidistantly from the two white LEDs at a distance of 65 cm in front of the body midline.

A trial started with the illumination of the fixation point. After 500 ms, the nociceptive stimulus was applied either unilaterally, on the left or the right hand, or bilaterally, i.e., on both hands simultaneously. The bilateral nociceptive stimulation condition was used as a control condition in which spatial attention was oriented unselectively to both hands. Such a neutral cueing control condition was chosen instead of a no-cue condition to control general alerting effects induced by the cues as a warning signal (see Raz and Buhle 2006). The unilateral stimulation condition was intended to orient spatial attention selectively to one of the two hands. The nociceptive stimulus was followed by a pair of visual stimuli of 5 ms duration each, one stimulus presented next to either hand (i.e., the left LED next to the left hand and the right LED next to the right hand). Depending on the block, the time interval between the onset of the nociceptive stimulus and that of the first visual stimulus of the pair was either 200, 400, or 600 ms. During a pre-testing session in which we tested a 150 ms interval, some of the participants perceived the first visual stimulus clearly before the nociceptive cue, an effect that can highly likely be accounted for by the slow velocity of the nociceptive input transmission. Twenty possible time intervals (SOAs for stimulus onset asynchronies) were used between the two visual stimuli of the pair: ±200, ±145, ±90, ±75, ±60, ±45, ±30, ±15, ±10, and ±5 ms (negative values indicate that the left LED was illuminated first). The participants were instructed to keep their gaze at the fixation point during the whole trial. In half of the blocks, participants had to respond verbally which of the two visual stimuli they perceived as occurring first (by answering 'left' or 'right'), while they had to respond which stimuli was perceived as second in the other half of the blocks. These two response modalities were used to dissociate a genuine perceptual spatial bias from a response/decisional bias (for a discussion, see Shore et al. 2001; Scharlau 2004; Spence and Parise 2010; Filbrich et al. 2016). The participant's response was encoded by the experimenter. No specific instruction was given regarding response speed. As soon as the response was encoded, illumination of the fixation point was switched off and the next trial started 2000 ms later. No feedback regarding the accuracy of participant's responses was given.

The experiment was composed of six blocks resulting from the combination of the time interval (200 vs. 400 vs. 600 ms) and the response modality ('which is first' vs. 'which is second'). The order of the blocks was pseudo-randomized for the different time intervals. The two blocks of the same time interval were performed consecutively, and the order of the different response modalities was randomized. Each block consisted of 3 series of 20 trials, one

for each cueing condition: unilateral left vs. unilateral right vs. bilateral nociceptive stimuli. The trials of the 3 series were randomly and equiprobably intermixed. Within each of the series, the presented SOAs were determined online for each trial according to the adaptive PSI procedure (Kontsevich and Tyler 1999), i.e., based on participants' performance on all previous trials within one cue condition (implemented through the Palamedes Toolbox, Prins and Kingdom 2009).

After each block, levels of perceived intensity of the nociceptive stimuli were assessed (on a scale from 0 to 10, with 0 = no sensation and 10 = very intense sensation) to ensure that IES were still perceived and that their intensities were rated as equivalent for both hands. If these criteria were not met, the intensities were adapted by increasing or reducing slightly the intensity of the stimuli, with 0.5 mA as a limit (see Favril et al. 2014 for details). If the limit was reached, the electrodes were displaced and the threshold measurements were restarted. A rest period between the blocks was possible when requested. Duration of the whole experiment was approximately 60 min.

Measures

For each participant and each condition, data were fitted with a logistic function, i.e., $f(x) = 1/(1 + \exp(-\beta(x - \alpha)))$, to derive the two measures of interest: the point of subjective simultaneity (PSS) and the slope. More in detail, we estimated these measures as the α (i.e. threshold) and β (i.e. slope) of the logistic function, respectively. In our study, the α 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). The β parameter describes the noisiness of the participant's performance, i.e., the precision or the variability of the participant's responses during the experiment (Kingdom and Prins 2010). The β, i.e., slope, has often been used to derive the just noticeable difference (JND) reported in TOJ studies. Too estimate the logistic function we used the PSI method (Kontsevich and Tyler 1999), in which the psychometric curve and its parameters are estimated at each trial. This specific method adapts the experimental procedure and the presented SOAs according to the performance of the participant on all the previous trials. The PSI method uses one of the most recent and complete adaptive algorithms and the main advantage with regard to other adaptive algorithms is that it allows targeting both the threshold and the slope, instead of a single point on the psychometric function (see Kingdom and Prins 2010). Specifically, the algorithm adopts a Bayesian framework, with the ultimate goal to estimate the posterior probability of the parameters of interest without probing extensively all the SOAs. The core idea is to minimize the expected entropy (i.e., uncertainty) of the posterior distribution trial by trial, such that the response of the participant at each trial provides the most information about the distribution of the parameters (distribution which has been initialized as a uniform distribution in a range of prior values which were chosen based on pilot experiments). In other words, the algorithm, given all the information at the previous trials, infers which condition (i.e., SOA) is the most informative to estimate the joint distribution of the parameters α and β. Notably, the distributions are shaped during the experiment considering all the previous trials, thus exploiting an adaptive approach. From the estimated joint posterior distribution, at each trial, the PSI method finds the best-fitting psychometric function to the responses collected on all of the previous trials (Kingdom and Prins 2010). Since a Bayesian approach is used in the present TOJ experiment, a prior probability distribution needs to be postulated, i.e., the researcher's knowledge/beliefs regarding the values of the parameters of interest (Kingdom and Prins 2010). We used a prior distribution of 0 ± 20 and 0.06 ± 0.6 for the threshold and slope parameters, respectively. Finally, another advantage of the present adaptive approach relies on the fact that not all the SOAs have to be tested extensively to estimate the values of the measures for each participant, thus reducing the total number of trials.

The average of the PSS values for left-sided cues and the values for right-sided cues (multiplied by −1 for the PSS for right-sided cues) was calculated to derive a unilateral cue condition for each participant and each experimental condition. Accordingly, for the unilateral cue condition, we plotted the proportion of trials in which the visual stimulus presented in the cued side of space was reported as appearing first as a function of SOA. For the bilateral cue condition, we plotted the proportion of trials in which the left visual stimulus was reported as appearing first as a function of SOA.

Data analysis

Before statistical analyses, data from the two response modalities ('which is first' and 'which is second') were merged to reduce potential response biases. To compare the mean scores of the maximal intensity of the nociceptive stimuli between both hands, a paired-sample t test was used. Self-reported mean intensities between the two hands were compared using

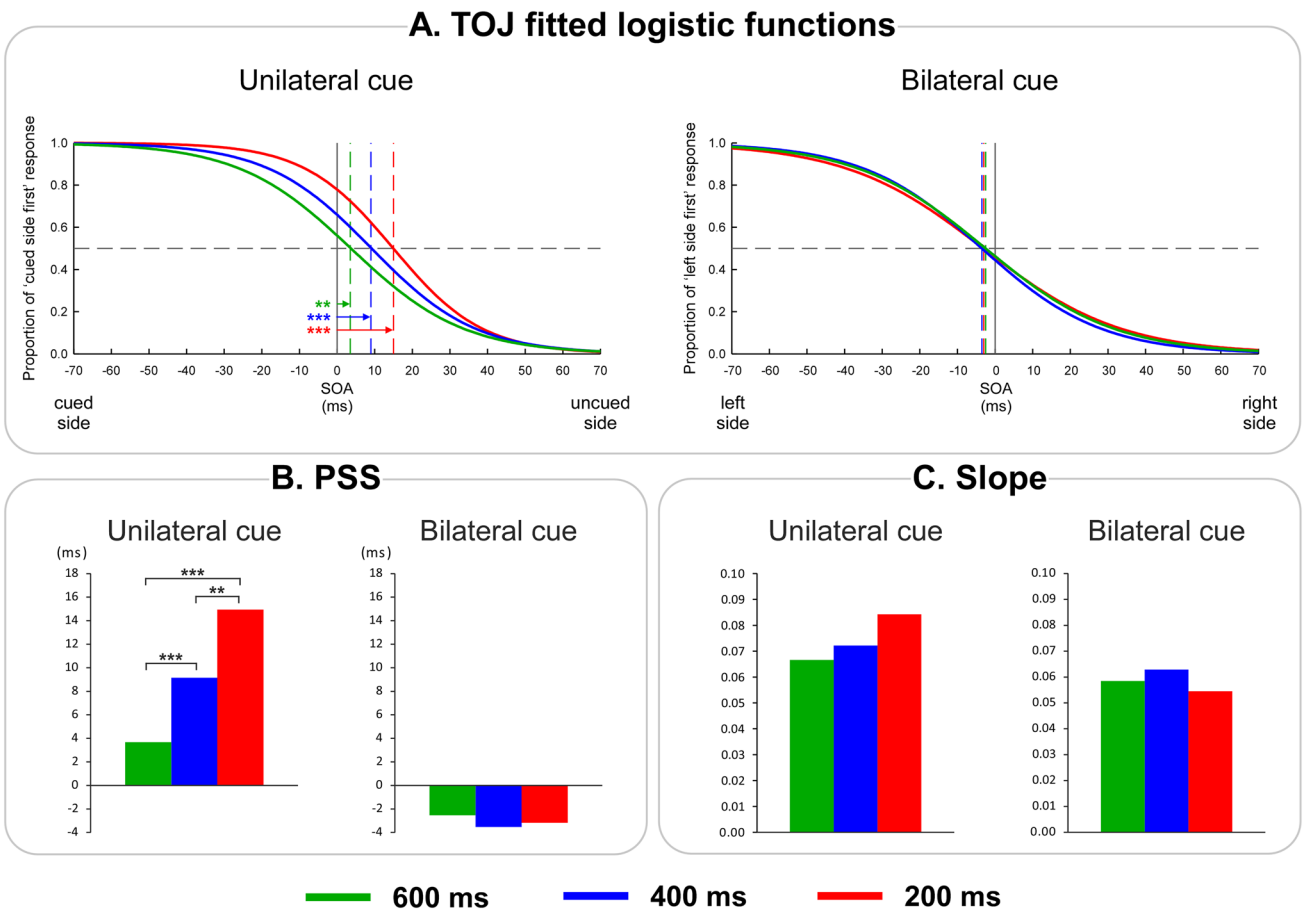


Fig. 1 Visual temporal order judgments (TOJs). (**A**) The fitted logistic functions from the data of the 15 participants for the unilateral and the bilateral cue conditions. For the *unilateral cue* condition, the *x*-axis represents different hypothetical SOAs between the two visual stimuli: *negative 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. For the *bilateral cue* condition, negative SOA values on the *x*-axis 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. The *lower sections* of the figure represent the PSS (**B**) and slope (**C**) values for the unilateral and the bilateral cue conditions. *Red curves* and *boxes* represent the conditions in which the time interval between the nociceptive cue and the first visual stimulus was 200 ms, *blue curves* and *boxes* represent the 400 ms interval, and *green curves* and *boxes* represent the 600 ms interval. The *arrows* in (**A**) indicate the PSS values significantly different from zero. Significant differences are indicated with *asterisks* (*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$)

a Wilcoxon signed-rank test. To characterize the existence of potential perceptual biases in TOJs in the different experimental conditions, each PSS value was compared to 0 using simple *t* tests. The effects of these conditions on PSS and slope were tested using an analysis of variance (ANOVA) for repeated measures with cue condition (unilateral vs. bilateral) and time interval (200 vs. 400 vs. 600 ms) as within-participant factors. Greenhouse–Geisser corrections of degrees of freedom and contrast analyses were used when necessary. Effect sizes were measured using Cohen's *d* (*t* tests) or partial Eta squared (ANOVA). Significance level was set at $p \leq 0.05$.

Results

Intensity of the nociceptive stimuli

The mean score of the maximal intensity of the nociceptive stimuli was 0.35 ± 0.09 mA for the left hand and 0.34 ± 0.09 mA for the right hand (no significant difference: $t(14) = 0.33$, $p = 0.75$). These values are in the range of intensities that have been shown to selectively activate nociceptors (Mouraux et al. 2010, 2013, 2014). The self-reported mean intensities were 4.47 ± 2.11 and 4.43 ± 1.93 for the left hand and the right hand, respectively, and the difference was not significant ($Z = -0.34$, $p = 0.73$).

PSS

The fitted psychometric curves and mean PSS data for each condition are illustrated in Fig. 1. Simple *t* tests revealed that PSS values were significantly different from zero for the unilateral cue condition for the 200 ms ($t(14)=6.99$, $p<0.001$, $d=1.80$), the 400 ms ($t(14)=4.87$, $p<0.001$, $d=1.25$), as well as the 600 ms ($t(14)=3.82$, $p=0.002$, $d=0.99$) time interval between the nociceptive and the visual stimuli. As for the bilateral cue condition, PSS values for none of the three time intervals were significantly different from zero (all $t(14) \leq -1.84$, $p \geq 0.09$) (see Fig. 1a). The PSS seems thus biased by the occurrence of a unilateral nociceptive stimulation.

The repeated-measures ANOVA revealed significant main effects for the factors *cue condition* ($F(1,14)=25.80$, $p<0.001$, partial eta^2 = 0.65) and *time interval* ($F(2,28)=7.21$, $p=0.003$, partial eta^2 = 0.34). The interaction between these two factors did also reach significance ($F(2,28)=7.22$, $p=0.003$, partial eta^2 = 0.34). Post-hoc analyses showed that there was a significant main effect of *time interval* for the unilateral ($F(2,28)=17.17$, $p<0.001$, partial eta^2 = 0.55) but not for the bilateral ($F(2,28)=0.10$, $p=0.91$, partial eta^2 = 0.007) cue conditions (see Fig. 1B). More specifically, in the unilateral cue condition, there was a significant difference between the 200 ms and the 400 ms time interval ($t(14)=2.53$, $p=0.024$, $d=0.65$), between the 200 ms and the 600 ms time interval ($t(14)=5.81$, $p<0.001$, $d=1.50$), as well as between the 400 ms and the 600 ms time interval ($t(14)=3.78$, $p=0.002$, $d=0.97$). The data suggest, therefore, an increasing shift of PSS with decreasing time interval between the nociceptive cue and the visual targets.

Slope

The mean slope data for each condition are shown in Fig. 1C. The two-way repeated-measures ANOVA revealed a significant main effect of cue condition ($F(1,14)=23.39$, $p<0.001$, partial eta^2 = 0.63) and a significant interaction between cue condition and time interval ($F(2,28)=3.69$, $p=0.038$, partial eta^2 = 0.21). There was no significant main effect for the factor time interval ($F(2,18)=0.88$, $p=0.43$, partial eta^2 = 0.06). Post-hoc analyses showed that the interaction between cue condition and time interval can be explained by the fact that there was a significant difference between the unilateral and the bilateral cue condition for the 200 ms interval ($F(1,14)=21.41$, $p<0.001$, partial eta^2 = 0.61) but not for the 400 and 600 ms intervals (all $F(1,14) \leq 2.47$, $p \geq 0.14$). These results suggest that participants' judgments were less noisy, i.e., less variable, in the unilateral than in the bilateral cue conditions when the time interval between the nociceptive cue and the first visual stimulus was 200 ms. This finding supports the PSS results reported above, as a steeper slope for the unilateral cue conditions for the 200 ms time interval could suggest that participant's judgments were more systematically biased by the nociceptive cues in this specific condition and thus more precise than in the other conditions.

Discussion

In the present studies, we showed for the first time that shifts in attention can be induced by a spatially non-predictive somatosensory stimulus that is specifically coded and transmitted by the nociceptive system. Indeed, the main aim of these studies was to demonstrate, by means of TOJ tasks, that a nociceptive stimulus can attract spatial attention to the side of external space corresponding to the limb on which the nociceptive stimulus is applied and prioritize the perceptual processing of visual stimuli that occur subsequently in this same side of space. Attentional prioritization in TOJ tasks is usually highlighted by shifts in the PSS (Spence and Parise 2010). In the present studies, participants judged the temporal order of pairs of visual stimuli, with one visual stimulus being presented next to either hand of the participants. With the aim to induce shifts in spatial attention, visual stimuli were shortly preceded by nociceptive stimuli which were applied on the participants' hands, either unilaterally on one of the two hands or bilaterally, on both hands simultaneously. The results showed that when both hands were stimulated simultaneously, none of the two visual stimuli were prioritized. As the bilateral cue condition was used as a control condition, no prioritization was actually expected, since attention was not selectively oriented to one specific spatial location. Conversely, when only one hand was stimulated, temporal order was judged to the advantage of the visual stimuli that were presented close to the hand on which the nociceptive stimulus was applied, as indexed by a shift of the PSS towards visual stimuli that occurred close to the hand that was not stimulated, i.e., the uncued side of space. More precisely, these uncued visual stimuli had to be presented several ms before the visual stimuli that occurred close to the stimulated hand, i.e., in the cued side of space, to be judged as occurring first. In addition, we showed that this attentional effect grew more efficient with the reduction of the time delay between the nociceptive cue and the first stimulus of the visual pair. The most significant effect was, indeed, observed with an interval of 200 ms.

Importantly, since in the present paradigm, all conditions were equivalently and randomly presented, the participants could not predict, based on the location of the unilateral nociceptive stimuli, the side of space in which the first stimulus of the visual pairs would appear. In other

words, the location of the nociceptive stimuli was uninformative as to the location of the forthcoming visual stimulus, suggesting that attention was attracted automatically by the nociceptive stimuli to their location, independently of voluntary control or decision of the participants. In the classic spatial attention literature, especially the one relating to cueing paradigms (e.g., Posner and Petersen 1990; Luck et al. 1994; Spence et al. 2004), attention can be spatially directed in two main ways: either endogenously, that is, by the participant's motivation, decision or anticipation, or exogenously, that is, driven by the stimulus itself, independently of the voluntary control of the participant. In endogenous cueing paradigms, attention displacements are manipulated by symbolic cues, i.e., cues that instruct the participant to shift his attention in one particular direction based on their meaning (such as an arrow), or, alternatively, using lateralized cues based on which the participant can anticipate the most probable location of the forthcoming target. For instance, in the study of Favril et al. (2014), after the application of a nociceptive stimulus on one hand, the visual stimuli appeared in the same side of space in 70% of the trials. Responses to these visual stimuli were characterized by faster reaction times and elicited evoked potentials (ERPs) of greater magnitude as compared to the responses to the 30% of visual stimuli that were delivered in the opposite side of space. One can imagine that if the proportion of trials "same vs. opposite sides of space" would have been reversed (i.e., visual stimuli occur in 70% of the trials in the space contralateral to the hand on which the nociceptive stimulus was applied), it could be highly expected that the results would also be reversed. In other words, faster reaction times and larger ERPs would have been observed for the visual stimuli presented in the opposite side, since, based on the location of the nociceptive stimulus, the participants would have predicted that it is most efficient to direct their attention to the opposite side of space. With exogenous cueing paradigms, in which all conditions are equiprobable, such predictions cannot be made and attention shifts are driven by the occurrence of the stimulus itself (Wright and Ward 1994). Exogenous cueing paradigms are useful to investigate mechanisms underlying crossmodal interaction (Spence et al. 2004), as they allow investigating how sensory inputs arising from different sensory modalities interact with each other to build a multisensory representation of space that integrates the body space and the external space proximal to the body (see Holmes and Spence 2004; Macaluso and Maravita 2010; di Pellegrino and Làdavas 2015). Such a multisensory representation is useful to adapt manipulation behaviours to innocuous stimuli (Rizzolatti et al. 1997) or defensive behaviours to noxious stimuli (Graziano and Cooke 2006). The existence of such a crossmodal representation of the body and the space nearby is hypothesized to rely on multimodal neurons in fronto-parietal regions that can respond to both somatosensory and visual stimuli occurring in the proximity of the body, as shown in non-human primate studies (Rizzolatti et al. 1981a, b; Dong et al. 1994). Surprisingly though, while visuo-tactile interactions have been investigated extensively (e.g., Spence and Driver 2004), visuo-nociceptive interactions are still poorly studied (Legrain and Torta 2015). For instance, besides the huge quantities of data regarding the recording of visuo-tactile neurons in monkeys (see e.g. Graziano et al. 2004), only one study recorded the activity of neurons responding to both thermo-nociceptive and visual stimuli (Dong et al. 1994). Yet, such visuo-nociceptive interactions are also clinically relevant, since it has been shown that some specific chronic pain conditions can impact the patients' abilities to represent and perceive space (see Legrain et al. 2012; Reinersmann et al. 2013). In addition, targeting these cognitive difficulties has been suggested as a potentially useful method to treat chronic pain. In a recent study, De Paepe et al. (2014) used similar TOJ tasks but with pairs of nociceptive stimuli, one stimulus applied on either hand. They showed that the occurrence, in one side of space, of a visual stimulus presented slightly before the pairs of nociceptive stimuli positively biased the perception of the nociceptive stimuli applied on the hand placed in the same side of space, to the detriment of the nociceptive stimuli applied to the opposite hand. Importantly, the impact of the visual cues was more efficient when they were presented close to the stimulated hand, as compared to the conditions in which they were presented farther away. In addition, they also showed that these effects were independent of the relative position of the hands in space (De Paepe et al. 2015). More precisely, when the participants crossed their hands over their body midline, the perception of the nociceptive stimuli applied to the left hand (but now located in right space) was positively impacted by right-sided visual stimuli. The reverse was shown for nociceptive stimuli applied to the right hand. These data strongly suggest that visual stimuli can affect the processing of nociceptive stimuli within the framework of a spatial representation integrating body space and proximal external space. The present studies showed the reverse effect, i.e., that nociceptive stimuli for their part can also positively impact spatially congruent visual stimuli. However, up to now, we are unable to conclude whether this effect is due to a general competition between the left and the right hemispaces, or more specifically to the existence of a multisensory representation of the body that not only integrates tactile, but also nociceptive, stimuli.

Before addressing the former question, a main issue was to determine in which time window nociceptive stimuli can positively impact the processing of stimuli from other sensory modalities, since the optimal time window in which such effects could be observed was completely unknown.

As already mentioned in the "Introduction" section, since the neural systems coding mechanical vs. nociceptive information are anatomically and functionally different, such estimation cannot rely on studies having used tactile stimuli as cues (e.g. Spence et al. 1998; Kennett et al. 2001). Pre-testing trials revealed that when using a time interval of 150 ms between the nociceptive cues and the visual targets, some participants perceived the nociceptive stimuli after the visual stimuli. This effect could be accounted for by the long distance from the coding receptors to the cortex and the slow velocity of the transmission system conveying nociceptive inputs. As a consequence, nociceptive inputs probably arrived, or were at least fully processed, at the cortical level after the visual inputs. We tested three time intervals between the nociceptive cue and the visual targets: 200, 400, and 600 ms. Results showed that biases induced by the unilateral nociceptive cues were significant for all three time intervals. It seems, therefore, that nociceptive stimuli can impact the processing of visual stimuli within a time window ranging from 200 to 600 ms. Analyses, however, also revealed that there were significant differences between the three intervals with regard to their ability to orient attention, showing increasing biases with decreasing time interval. The 200 ms time interval between the nociceptive cue and the first visual target was thus the most efficient for the nociceptive cue to capture attention and facilitate the processing of subsequent visual stimuli presented in the same side of space. Now, that we highlighted the optimal time window to obtain cueing effects from nociceptive stimuli on visual stimuli, future studies should also investigate whether the crossmodal influence of nociception on visual processing depends on a multisensory reference frame for the spatial perception of sensory events that is organized around the body.

Finally, another major contribution of the present studies is that we were able to demonstrate crossmodal shifts in spatial attention using a TOJ task based on the adaptive PSI procedure (Kontsevich and Tyler 1999). The advantage of this method is that the PSS and the slope are estimated at each trial, and that the to-be-tested SOAs on each trial depend on the participant's own performance on all the previous trials, contrary to the classically used method of constant stimuli in which all the SOAs have to be presented several times to finally estimate the PSS and slope values. Since with the adaptive method, not all the possible SOAs have to be tested to derive the final measures for each participant; the number of necessary trials can be largely reduced. This can be of interest when an important number of conditions need to be tested (see De Paepe et al. 2014). Maintaining a precise estimation of TOJ parameters while reducing the number of trials is also of particular interest for the assessment of perceptual difficulties in clinical populations, whose performance could, due to their clinical conditions, particularly be prone to be influenced by task-independent factors as fatigue or difficulties in sustained attention. Furthermore, using the adaptive method can also be of interest to minimize the risk of imprecise estimates of the measures due to inappropriately chosen stimulus levels (SOAs). With this method, one can consider to include a broader range of SOAs levels (without extending the duration of the experiment) to minimize floor or ceiling effects when there is no a priori knowledge based on pilot studies or previous research as to the range of SOAs used to reliably estimate the measures of interest. For example, Van der Biest and colleagues (unpublished) used a tactile TOJ paradigm based on the method of constant stimuli to assess perceptual deficits in chronic pain patients. They could, however, not reliably evidence any biases, since, for an important number of participants, the magnitude of the bias, as well as the SOA at which participants judge stimulus order correctly in 75% of trials was bigger than the highest presented SOA, which suggests that the chosen SOA levels were probably not adapted and that possible effects could have been masked by the difficulty of the task. Using the adaptive PSI method, we recently succeeded to demonstrate subtle visuospatial biases in a TOJ task in patients suffering from unilateral chronic pain (Filbrich et al. submitted for publication). Using adaptive methods seems, therefore, to be efficient in minimizing undesired confounding effects in the interpretation of TOJ data, especially when comparing conditions with different levels of difficulty or different populations.

To conclude, the present studies succeeded to demonstrate the efficiency of our paradigm, that is, a crossmodal cueing temporal order judgment task based on an adaptive procedure, with the aim to further investigate multisensory interaction between nociception and vision, both in healthy volunteers and chronic pain patients.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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