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

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## **Abstract**

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

*Keywords:* nociception; vision; crossmodal; gaze shift; remapping; peripersonal

61

## 1. Introduction

62 The cognitive mechanisms, and their neuronal substrates, underlying crossmodal  
63 interaction between somatic and non-somatic stimuli have been largely investigated over the  
64 last decades (see e.g. di Pellegrino & Làdavas, 2015; Holmes & Spence, 2004; Macaluso &  
65 Maravita, 2010). For such crossmodal interactions between somatic and non-somatic stimuli  
66 to be possible, one needs to be able to coordinate and to integrate the representation and the  
67 perception of the space of the body and those of its surrounding space. Conceptualized by the  
68 notion of peripersonal reference frames (Rizzolatti, Fadiga, Fogassi, & Gallese, 1997), such  
69 integrated and multisensory representations are coordinate systems for the spatial coding of  
70 both somatic and extra-somatic (e.g. visual) stimuli occurring near the body. Such systems are  
71 thought to be used as interfaces to translate the perceptual characteristics of an object near the  
72 body into a motor schema to spatially guide actions toward that object, such as grasping and  
73 dexterous manipulation (Brozzoli, Ehrsson, & Farne, 2014). It has been further hypothesized  
74 that such peripersonal representations could be used for the purpose of defensive actions  
75 against objects that threaten the physical integrity of the body (Cooke & Graziano, 2004;  
76 Graziano & Cooke, 2006). Supporting this latter hypothesis, recent studies in humans  
77 demonstrated a privileged interaction between visual stimuli occurring very close to the body,  
78 and nociceptive stimuli, that is, stimuli that selectively activate the nervous system  
79 specifically involved in coding and transmitting information about sensory events that have  
80 the potential to inflict body damage (see Legrain & Torta, 2015 for a review). Whereas the  
81 reference frames involved in tactile processing and the mechanisms underlying visuo-tactile  
82 interactions have been studied with a wide variety of tasks (e.g., di Pellegrino & Làdavas,  
83 2015; Spence, Pavani, & Driver, 2004; Tamé, Wühle, Petri, Pavani, & Braun, 2017), most of  
84 the studies investigating visual-nociceptive interactions used temporal order judgment (TOJ)  
85 tasks. These tasks consist in presenting pairs of stimuli with various time delays between  
86 them, and participants have to report which of the two stimuli they perceived as having been  
87 presented first. In such tasks, the amount of time one stimulus has to follow or precede the  
88 other in order for the two stimuli to be perceived by the participant as occurring  
89 simultaneously is used as an index of attentional bias, and can be shifted to the advantage of  
90 one of the two stimuli (Spence & Parise, 2010). Indeed, according to the theory of prior entry  
91 (Titchener, 1908), paying attention to a stimulus speeds-up its processing as compared to a  
92 competing unattended stimulus. A first series of experiments in which pairs of nociceptive  
93 stimuli were used, one applied on each hand dorsum, showed that judgments about the  
94 occurrence of nociceptive stimuli were dependent on the relative position of the hands in  
95 external space (De Paepe, Crombez, & Legrain, 2015; Sambo et al., 2013). When TOJ tasks  
96 were performed with the hands crossed over the midsagittal plane of the body, judgments  
97 were much less accurate, as compared to conditions in which the task was performed with a  
98 normal, uncrossed hand posture. These results suggest that the ability of perceiving  
99 nociceptive stimuli is not only determined by the anatomical position of the stimuli on the  
100 body, but also relies on frames of reference that integrate the relative position of the  
101 stimulated limb in external space (see Smania & Aglioti, 1995). Similar effects have been  
102 reported for tactile stimuli (Shore, Spry, & Spence, 2002; Yamamoto & Kitazawa, 2001). In  
103 further experiments, the nociceptive stimuli were preceded by a visual cue presented  
104 randomly in the same side of space as one of the hands (De Paepe et al., 2015; De Paepe,  
105 Crombez, Spence, & Legrain, 2014). These studies showed that the occurrence of the visual  
106 stimulus biased judgments in favor of the perception of the nociceptive stimuli applied on the  
107 hand laying in the same side of space as the visual stimulus. The effects were shown to be  
108 stronger for the visual stimulus presented the closest to the stimulated hand (De Paepe et al.,  
109 2014), independently of the relative position of the hands and the visual stimuli according to

110 the participant's trunk (De Paepe et al., 2015). In other words, the ability of a visual stimulus  
111 to impact the perception of a nociceptive stimulus depends on the proximity of the visual  
112 stimulus to the limb on which the nociceptive stimulus is applied and thus on the location of  
113 the stimulated hand in external space, irrespective of the fact which hand was stimulated  
114 according to an anatomical reference (De Paepe et al., 2015). Taken together, these studies  
115 suggest the existence of a peripersonal frame of reference for the localization of nociceptive  
116 stimuli, thus enabling close visual stimuli in external space to affect the perception of  
117 nociceptive stimuli applied on the body.

118         There are longstanding debates on the mechanisms underlying crossmodal interaction  
119 between somatic and proximal non-somatic stimuli (Macaluso, Frith, & Driver, 2001;  
120 McDonald, Teder-Sälejärvi, & Ward, 2001; Spence, McDonald, & Driver, 2004). One of the  
121 most popular theories postulates that such interactions rely on the existence of neurons able to  
122 respond to both somatic and non-somatic stimuli (see Graziano, Gross, Taylor, & Moore,  
123 2004 for a review). More precisely, electrophysiological studies in monkeys have revealed,  
124 mostly in the ventral premotor cortex (PMv) and ventral intraparietal sulcus (VIP), the  
125 existence of neurons associating tactile and visual receptive fields (RFs). The particularity of  
126 these visual RFs is that they are often limited and anchored to the body parts which *host* their  
127 associated tactile RFs, thus following these limbs during their movements in space. In other  
128 words, the tactile and the visual RFs are aligned according to a frame of reference that takes  
129 into account external space, instead of their initial and respective anatomical frames of  
130 reference (i.e. somatotopic and retinotopic, respectively). Several studies have shown, for  
131 instance, that PMv neurons respond to both visual and tactile stimuli only when the position  
132 or the trajectory of the visual stimulus is spatially congruent with the limb on which it is  
133 anchored and thus with its associated tactile RF, irrespective of the posture of the body and  
134 the projection of the visual stimulus onto the retina (Fogassi et al., 1992; Fogassi et al., 1996;  
135 Gentilucci, Scandolara, Pigarev, & Rizzolatti, 1983; Graziano, Hu, & Gross, 1997; Graziano,  
136 Yap, & Gross, 1994). Indeed, Graziano et al. (1997) have shown that visual stimuli were still  
137 able to activate such bimodal neurons even when the monkeys were trained to fixate their  
138 gaze at different positions. Similar effects have been observed in neuroimaging studies  
139 performed in humans (see Macaluso & Maravita, 2010). For instance, Macaluso and  
140 colleagues investigated how cortical responses to a stimulus of one sensory modality can be  
141 influenced by the proximal occurrence of a stimulus of another sensory modality (Macaluso,  
142 Frith, & Driver, 2000; Macaluso, Frith, & Driver, 2002). In one of their studies, participants  
143 were asked to place one hand, on which tactile stimuli were applied, close to a visual  
144 stimulus, and, across conditions, to fixate their gaze either to the left or to the right of the  
145 visual stimulus and the stimulated hand (Macaluso et al., 2002). Using such a manipulation,  
146 the visual stimulus was alternately seen in different visual hemifields, while the tactile  
147 stimulus was always felt on the same hemibody. The occurrence of a tactile stimulus was  
148 shown to boost the cortical responses to the visual stimuli in the visual cortex contralateral to  
149 visual stimuli location, independently of the primary cortical projection of the tactile input to  
150 its contralateral hemisphere, and thus irrespective of the hemispheric correspondence between  
151 the visual and the tactile cortical projections (Macaluso et al., 2002).

152         The studies reviewed here above suggest that one of the mechanisms underlying  
153 crossmodal interaction between somatic and non-somatic stimuli relies on the ability to  
154 update the mapping coordinates from the initial anatomical reference frames of each sensory  
155 modality (i.e. somatotopic for somatosensory inputs and retinotopic for visual inputs) to an  
156 integrated mapping system using external space as main reference frame. They also suggest  
157 that such an updating takes into account the relative position of the limbs and the eyes,  
158 whatever the stimulated hemibody and hemifield. In the present study, we investigated

159 whether nociceptive stimuli can influence the perception of visual stimuli, especially those  
160 presented close the limb on which the nociceptive stimuli are felt. This question is of  
161 particular importance when considering that it has been suggested that chronic pain states  
162 could change how patients perceive their visual environment (see e.g. Legrain, Bultitude, De  
163 Paepe, & Rossetti, 2012). More specifically, we investigated whether such an interaction  
164 between nociceptive and visual stimuli depends on the relative spatial congruence between  
165 the location of the nociceptive stimuli (i.e. of the stimulated limb) and that of the visual  
166 stimuli, irrespective of their exact positions according to their respective sensory RFs (i.e. the  
167 congruence of their respective anatomical reference frames). To this end, we manipulated the  
168 direction of the gaze so that visual stimuli and the body part on which nociceptive stimuli  
169 were applied could be seen in different areas of the visual field, while the cortical projections  
170 of the nociceptive inputs remained constant (as it was always the same limb that was  
171 stimulated). Participants performed TOJs on pairs of visual stimuli, one centrally positioned  
172 in front of the participant and one more laterally. One of the hands was placed close to the  
173 central visual stimulus, and nociceptive stimuli could occasionally be applied on that specific  
174 hand. Using such a setting, the central visual stimuli were therefore always the ones spatially  
175 congruent with the nociceptive stimuli. However, by changing gaze direction across the  
176 experimental blocks, central visual stimuli could either appear as left-sided stimuli (i.e. in the  
177 left visual hemifield) when participants' gaze was shifted toward the right side of space, or as  
178 right-sided stimuli (i.e. in the right visual hemifield) when gaze was shifted to the left side.  
179 We hypothesized that if nociception influences vision based on their spatial correspondence in  
180 external space, nociceptive stimuli would bias visual TOJs in favor of the perception of the  
181 visual stimuli presented close to the stimulated hand, i.e., the centrally positioned visual  
182 stimuli, independently of left vs. right gaze direction. In other words, the visual hemifield (left  
183 vs. right) that would be prioritized by the occurrence of the nociceptive stimuli should be  
184 reversed as function of the change in gaze direction. Such a result would also corroborate the  
185 hypothesis that somatic, including nociceptive, and non-somatic stimuli are remapped from  
186 their respective initial frames of reference into a common frame that uses the space around the  
187 body as reference.

188

## 189 **2. Methods**

### 190 **2.1. Participants**

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

205           **2.2.           Stimuli and apparatus**

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

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

230           **2.3.           Procedure**

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

247           Before each experimental block, participants were told whether to fixate their gaze at  
248 the left or the right fixation LED – without moving their head – so that the central LED and  
249 the hand on which nociceptive stimuli could be applied were either seen in the participants’  
250 right visual hemifield (RVF) in case of left fixation, or in their left visual hemifield (RVF) in  
251 case of right fixation. A trial started with the illumination of the fixation LED and after 500

252 ms, participants either received a nociceptive stimulus applied on the hand (cue condition) or  
253 no stimulation (no cue condition). The condition without nociceptive stimulation was  
254 introduced to control for effects on visual perception due to the mere presence of a hand that  
255 could potentially attract attention to its position (e.g. Lloyd, Azanon, & Poliakoff, 2010; Reed,  
256 Grubb, & Steele, 2006) instead of the nociceptive cues. Two hundred ms (Filbrich, Alamia,  
257 Burns, & Legrain, 2017) after the potential onset of the nociceptive stimulation, a pair of  
258 visual stimuli (the left LED and the central LED in case of left fixation or the central LED and  
259 the right LED in case of right fixation), both stimuli of 5 ms duration each, was presented.  
260 Twenty possible time intervals (SOAs, i.e. stimulus onset asynchronies) were used between  
261 the two visual stimuli:  $\pm 200$ ,  $\pm 145$ ,  $\pm 90$ ,  $\pm 75$ ,  $\pm 60$ ,  $\pm 45$ ,  $\pm 30$ ,  $\pm 15$ ,  $\pm 10$ ,  $\pm 5$  ms (negative  
262 values indicate that the LED in the LVF was illuminated first, positive values that the one in  
263 the RVF was illuminated first). Participants were instructed to keep their gaze at the fixation  
264 point during the whole trial. Depending on the block, they either reported verbally which of  
265 the two visual stimuli they perceived as appearing first, or they reported which visual stimulus  
266 they perceived as appearing second (by answering ‘*left*’ or ‘*right*’, corresponding to the LVF  
267 and the RVF, respectively). Using these two response modalities allows minimizing the  
268 contribution of response and/or decision-related biases to the perceptual spatial biases that are  
269 investigated (for details see e.g. Filbrich, Torta, Vanderclausen, Azanon, & Legrain, 2016;  
270 Shore, Spence, & Klein, 2001; Spence & Parise, 2010). The participants didn’t receive any  
271 specific instruction regarding response speed, as well as no feedback regarding the accuracy  
272 of their performance. Illumination of the fixation point was switched off as soon as the  
273 response was encoded by the experimenter and the next trial started 2000 ms later. A rest  
274 period between the blocks was possible when requested. Duration of the whole experiment  
275 was approximately 45 min.

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

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

## 294 **2.4. Measures**

295 To assess the performance of the participants in the TOJ task we consider two  
296 measures: the point of subjective simultaneity (PSS) and the slope. In the present study, these  
297 two measures were estimated as the  $\alpha$  and  $\beta$  parameters of a logistic function, i.e.  $f(x) =$   
298  $\frac{1}{1+\exp(-\beta(x-\alpha))}$ , respectively, which was fitted to the data for each participant and each



299 condition. The  $\alpha$  defines the threshold of the psychometric function. In our study, this  
300 threshold corresponds to the SOA at which the two visual stimuli are perceived as occurring  
301 first equally often (i.e. the 0.5 criterion on the ordinate). Accordingly, this measure  
302 corresponds to the PSS which is defined as the amount of time one stimulus has to precede or  
303 follow the other in order for the two stimuli to be perceived by the participant as occurring  
304 simultaneously (Spence, Shore, & Klein, 2001). The  $\beta$  parameter defines the slope of the  
305 logistic function, which describes the noisiness of the results and can be related to the  
306 precision, i.e. variability, of the participants' responses during a condition (Kingdom & Prins,  
307 2010). The psychometric curve and its parameters were estimated at each trial, since we used  
308 the adaptive PSI method (Kontsevich & Tyler, 1999) to adapt the experimental procedure and  
309 the presented SOAs, which is based on an algorithm that adopts a Bayesian framework (for a  
310 detailed description of how the logistic function is estimated and the advantages of using the  
311 adaptive PSI method in TOJ, see Filbrich, Alamia, Burns et al., 2017)

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

## 315 **2.5. Data analysis**

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

331

## 332 **3. Results**

### 333 **3.1. Intensity of nociceptive stimuli**

334 The mean of the maximal intensities was  $0.30 \pm 0.09$  mA for nociceptive stimuli  
335 applied to the right hand and  $0.30 \pm 0.11$  for nociceptive stimuli applied to the left hand (no  
336 significant difference:  $t(18) = 0.00, p = 1$ ). These intensities are in the range of values that have  
337 been shown to selectively activate skin nociceptors in previous studies (Mouraux et al., 2013;  
338 Mouraux et al., 2010; Mouraux et al., 2014). The means of the self-reported intensities before  
339 the first block were  $5.4 \pm 2.17$  and  $5 \pm 2.31$  for the right and the left hand, respectively (no  
340 significant difference:  $U = 46.5, p = 0.796$ ). Means of the self-reported mean intensities across  
341 the four blocks were  $4.72 \pm 2.18$  and  $4.32 \pm 2.04$  for the right and the left hand, respectively (no  
342 significant difference:  $U = 46.5, p = 0.796$ ).

### 343 3.2. PSS

344 Results are illustrated in Fig. 2. In the conditions with nociceptive cue, one-sample t-  
345 tests showed that PSS values were positive ( $14.99 \pm 20.23$ ) and significantly different from  
346 zero ( $t(19) = 3.31, p = 0.004, d = 0.74$ ) when gaze was directed to the right (and, therefore,  
347 central LED and hand in the LVF). However, when gaze was directed to the left (central LED  
348 and hand in RVF), PSS values tended to be more negative ( $-5.57 \pm 20.43$ ) but not significantly  
349 different from 0 ( $t(19) = -1.22, p = 0.283$ ). For the no cue condition, neither PSS values for the  
350 left gaze direction nor for the right gaze direction were significantly different from zero (all  
351  $t(19) \leq 0.81, p \geq 0.43$ ). When gaze was directed to the right, visual stimuli appearing in the  
352 RVF (i.e. the uncued side of space) had thus to be presented significantly earlier than stimuli  
353 appearing in the LVF (i.e. the cued side of space) to have the chance to be perceived as  
354 occurring simultaneously.

355 The ANOVA revealed a significant interaction between *cue condition* and *gaze*  
356 *direction* ( $F(1,18) = 18.06, p \leq 0.001, \eta_p^2 = 0.50$ ). Contrast analyses showed that, during left  
357 fixation, the PSS value was significantly smaller in the cue than in the no cue condition  
358 ( $F(1,19) = 5.62, p = 0.029, \eta_p^2 = 0.23$ ). On the contrary, during right fixation, the PSS value was  
359 significantly larger in the cue than in the no cue condition ( $F(1,19) = 18.13, p \leq 0.001, \eta_p^2 =$   
360  $0.49$ ). In addition, the PSS values of the cue conditions were significantly different between  
361 left and right fixation conditions ( $F(1,19) = 9.65, p = 0.006, \eta_p^2 = 0.34$ ), whereas such a  
362 comparison revealed quite identical values in the no cue conditions ( $F(1,19) = 0.02, p = 0.90,$   
363  $\eta_p^2 = 0.00$ ). In the conditions during which nociceptive stimuli were applied on the hand,  
364 spatial biases changed direction according to gaze fixation: when the gaze was directed to the  
365 left, temporal order was judged to the advantage of stimuli in the RVF, whereas it was judged  
366 to the advantage of stimuli in the LVF when gaze was directed to the right. In other words,  
367 judgments were always biased to the advantage of the visual stimuli the closest to the hand on  
368 which the nociceptive stimuli were applied, irrespective of the visual hemifield in which they  
369 were seen. The between-participant factor *hand* was also significant ( $F(1,18) = 7.55, p = 0.013,$   
370  $\eta_p^2 = 0.30$ ), suggesting that biases were larger when the left hand ( $M = 10.30, SD = 23.05$ ) was  
371 placed next to the central LED than when the right hand ( $M = -3.09, SD = 15.90$ ) was placed  
372 there. None of the main effects and no interaction with the between-participant factor were  
373 significant (all  $F \leq 3.07, p \geq 0.097$ ).

### 374 3.3. Slope

375 Results are illustrated in Fig. 2. The ANOVA revealed a significant interaction  
376 between *cue condition* and *gaze direction* ( $F(1,18) = 8.17, p = 0.010, \eta_p^2 = 0.31$ ). None of the  
377 main effects or any of the interactions with the between-participant factor *hand* were  
378 significant (all  $F \leq 1.96, p \geq 0.178$ ). However, none of the contrasts we performed could  
379 explain the *cue x gaze direction* interaction (all  $F \leq 2.81, p \geq 0.101$ ). This suggests that the  
380 precision of the participants' responses does not seem to be affected differently neither in the  
381 left vs. right fixation condition as a function of cue condition, nor in the cue vs. no cue  
382 conditions as a function of gaze direction.

### 383 4. Discussion

384 The aim of the present experiments was to study the effect of the spatial alignment  
385 between nociceptive and visual stimuli according to the relative spatial position of their  
386 respective receptive fields on nociceptive-visual interactions. Such effects of spatial alignment  
387 have usually been investigated using the crossed-hands procedure during which stimuli are

388 applied when the hands are crossed over the body midline (e.g. De Paepe et al., 2015; Eimer,  
389 Cockburn, Smedley, & Driver, 2001; Kennett, Eimer, Spence, & Driver, 2001; Kennett,  
390 Spence, & Driver, 2002; Shore et al., 2002; Yamamoto & Kitazawa, 2001). Using such a  
391 procedure, the left and right sides of space are defined for both somatic and extra-somatic  
392 stimuli according to a trunk-based reference. Hence, hemispaces (for extra-somatic stimuli)  
393 and hemibodies (for somatic stimuli) are defined according to the same reference axis (i.e. the  
394 trunk/head). Here, we investigate the effects of spatial alignment by manipulating current  
395 gaze direction. Manipulating gaze direction could be considered as being slightly different  
396 from the classical crossed-hands procedure, in the sense that, with this procedure, the  
397 representations of the different stimuli in terms of left vs. right side of space can be defined  
398 according to different reference axes. Indeed, whereas the visual stimuli and the stimulated  
399 hand were either seen in the left or the right hemifield (i.e. hemisphere) according to an eye-  
400 centered reference, the stimulated hemibody (i.e. the hand) was still defined according to a  
401 reference centered on the trunk. Consequently, manipulating gaze direction while keeping the  
402 position of the head constant entails that in some trials spatially congruent nociceptive and  
403 visual stimulations occur in one visual hemifield, while in other trials such spatially congruent  
404 multimodal stimulations occur in the opposite hemifield according to an eye-centered  
405 reference, despite the fact that the physical positions of the visual stimuli and the hand on  
406 which the nociceptive stimulus was applied remain unchanged according to a trunk-centered  
407 reference (see Macaluso et al., 2002 for a similar procedure with tactile stimuli). In the  
408 present study, we aimed to demonstrate that the influence of nociception on visual perception  
409 is strongest when nociceptive and visual stimuli are congruent in external space, i.e. seen in  
410 the same hemifield, independently of the direction of gaze, and independently of the  
411 anatomical congruence between the stimulated hemibody and the stimulated visual hemifield.  
412 This hypothesis was tested by using TOJ tasks. In the present experiment, shifts of the PSS in  
413 the perception of visual stimuli were aimed to be induced by nociceptive cues presented in  
414 one side of space. Results showed that for both gaze direction conditions, biases were more  
415 important in the conditions with a nociceptive cue than in conditions without nociceptive cue,  
416 suggesting that a nociceptive stimulus can impact visual perception. Importantly, when a  
417 nociceptive cue was applied on the centrally placed hand, the direction of the bias changed  
418 according to the gaze direction, showing that participants' TOJs prioritized the perception of  
419 visual stimuli presented in the RVF when gaze was directed to the left (i.e. the stimulated  
420 hand is seen in the RVF), whereas they prioritized the perception of visual stimuli presented  
421 in the LVF when gaze was directed to the right (i.e. the stimulated hand is seen in the LVF).  
422 Thus, participants always prioritized the visual stimuli presented close to the stimulated hand,  
423 irrespective of the gaze direction.

424 It has to be noted however that, even if there was a significant difference in the biases  
425 between conditions with cue and conditions without cue for both left and right gaze  
426 conditions, biases to the advantage of visual stimuli presented close to the nociceptive  
427 stimulus in the cue conditions were only significantly different from zero when gaze was  
428 directed to the right (i.e. when the stimulated hand was seen in the LVF). This could be  
429 explained by a slight *general* bias to the LVF that would even be present when spatial  
430 attention is not explicitly manipulated by the presence of nociceptive cues. Such systematic  
431 left-ward biases in visuospatial attention, termed *pseudoneglect*, are a well-described  
432 phenomenon in neurologically intact participants (see e.g. Bowers & Heilman, 1980; Brooks,  
433 Della Sala, & Darling, 2014; Jewell & McCourt, 2000; Voyer, Voyer, & Tramonte, 2012).  
434 Although the left-ward biases in the no cue condition were not significantly different from  
435 zero, one could still imagine a possible influence on the crossmodal effects. Such a *general*  
436 bias to the LVF could enhance biases to the advantage of the visual stimulus in the LVF,  
437 induced by the spatial correspondence of the nociceptive stimulus in the same hemifield,

438 when gaze was directed to the right, while it could reduce biases to the advantage of the RVF,  
439 induced by the presence of the nociceptive stimulus in same hemifield, when gaze was  
440 directed to the left. Importantly however, we showed that a nociceptive stimulus seen in the  
441 RVF can induce biases to the advantage of visual stimuli in the RVF, thus counterbalancing  
442 the possible influence of a *general* bias to the LVF (by changing the direction of the bias).  
443 Thus, even if biases to the advantage of the visual stimuli presented close to the stimulated  
444 hand (in the RVF) when gaze was directed to the left were not significantly different from  
445 zero, this finding doesn't change the fact that we were able to demonstrate that the perception  
446 of a visual stimulus can be impacted by a nociceptive stimulus applied on a hand that is seen  
447 in the same hemifield, that is, when both stimuli are presented in the same location in external  
448 space.

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

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

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

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

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

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

580

581

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772

## Figure captions

774 **Fig. 1. Design of the experiment.** Visual stimuli are presented by means of three white  
 775 LEDs, one placed centrally in front of the participants and two other ones, one placed to the  
 776 left and one placed to the right of the central LED. The task-relevant pair for each condition is  
 777 represented by the white circles with a small yellow halo, and always consists in a visual  
 778 stimulus seen in the left visual hemifield (LVF) and a visual stimulus seen in the right visual  
 779 hemifield (RVF). Either the left or the right hand, counterbalanced between participants, is  
 780 placed next to the central LED. Nociceptive cues are illustrated by the red flashes, and are  
 781 occasionally applied on the centrally placed hand, shortly preceding the visual stimuli.  
 782 Depending on the condition, participants either fixated their gaze, without moving their head,  
 783 at a left or a right fixation point, which are both represented by the yellow circles.  
 784 Accordingly, the potentially stimulated hand is either seen in the RVF or in the LVF,  
 785 respectively. The LED expected to be prioritized during TOJs in the different conditions is  
 786 encircled by the large rose halo.

787 **Fig. 2. Averaged results of the 20 participants.** The upper part of the figure (A) depicts the  
 788 fitted logistic functions for the *left gaze direction* and the *right gaze direction* conditions. The  
 789 x-axis represents different hypothetical stimulus onset asynchronies (SOAs) between the two  
 790 visual stimuli: negative values indicate that the visual stimulus in the left visual hemifield  
 791 (LVF) was presented first, while positive values indicate that the visual stimulus in the right  
 792 visual hemifield (RVF) was presented first. The y-axis represents the proportion of trials in  
 793 which the participants perceived the visual stimulus in the LVF as occurring first. For both  
 794 left gaze direction and right gaze direction conditions, red dashed curves represent the  
 795 conditions in which no nociceptive cue was applied on the centrally placed hand, with the  
 796 corresponding PSS values indicated by the red vertical dashed lines. Blue solid curves  
 797 represent the conditions in which a nociceptive cue was applied on the hand, with the  
 798 corresponding PSS values indicated by the blue vertical dashed lines. The blue arrow in the  
 799 *right gaze direction* condition indicates the PSS value significantly different from zero. In this  
 800 condition, when a nociceptive cue was applied, curves are shifted to the RVF, indicating that  
 801 visual stimuli presented in the RVF had to be presented several ms before the visual stimuli  
 802 presented in the LVF (i.e. the one spatially congruent with the stimulated hand) to have the  
 803 chance to be perceived as occurring first equally often. The lower parts of the figure illustrate  
 804 the mean PSS (B) and slope (C) values, for both the *left gaze direction* and the *right gaze*  
 805 *direction* conditions. Significant differences are indicated with asterisks (\*  $p \leq .05$ , \*\*  $p \leq .01$ ,  
 806 \*\*\*  $p \leq .001$ ). Error bars represent the 95% confidence intervals adapted according to the  
 807 method of Cousineau (2005).