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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 ± 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 δ nociceptors, without co-activation of A β 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: ± 200 , ± 145 , ± 90 , ± 75 , ± 60 , ± 45 , ± 30 , ± 15 , ± 10 , ± 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 α and β 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 α 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 β 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 ± 0.09 mA for nociceptive stimuli
335 applied to the right hand and 0.30 ± 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 ± 2.17 and 5 ± 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 ± 2.18 and 4.32 ± 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 ± 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 ± 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 δ -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.

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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).