

## **Perceptual simultaneity between nociceptive and visual stimuli depends on their spatial congruence**

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## Abstract

To protect our body against physical threats, it is important to integrate the somatic and extra-somatic inputs generated by these stimuli. Temporal synchrony is an important parameter determining multisensory interaction, and the time taken by a given sensory input to reach the brain depends on the length and conduction velocity of the specific pathways through which it is transmitted. Nociceptive inputs are transmitted through very slow conducting unmyelinated C and thinly myelinated A $\delta$  nociceptive fibers. It was previously shown that to perceive a visual stimulus and a thermo-nociceptive stimulus applied on the hand as coinciding in time, the nociceptive stimulus must precede the visual one by 76 ms for nociceptive inputs conveyed by A $\delta$  fibers and 577 ms for inputs conveyed by C fibers. Since spatial proximity is also hypothesized to contribute to multisensory interaction, the present study investigated the effect of spatial congruence between visual and nociceptive stimuli. Participants judged the temporal order of visual and nociceptive stimuli, with the visual stimuli flashed either next to the stimulated hand or next to the opposite unstimulated hand, and with nociceptive stimuli evoking responses mediated by either A $\delta$  or C fibers. **The amount of time by which the nociceptive stimulus had to precede the visual stimulus for them to be perceived as appearing concomitantly** was smaller when the visual stimulus occurred near the hand receiving the nociceptive stimulus as compared to when it occurred near the contralateral hand. This illustrates the challenge for the brain to process the synchrony between nociceptive and non-nociceptive stimuli to enable their efficient interaction to optimize defensive reaction against physical dangers.

**Keywords:** Nociception, Pain, vision, multisensory, temporal order judgment, space.

## 1        **1. Introduction**

2        Surrounding objects with which we interact are often perceived through different sensory  
3 modalities. Hence, proper coordination between the different sensory modalities is crucial  
4 to optimize integration of their respective inputs, generate a coherent percept, and trigger  
5 appropriate behavioral responses. This is particularly achieved when different sensory  
6 stimuli occur close in time (Meredith, Nemitz, & Stein, 1987; Spence & Squire, 2003; Stein &  
7 Meredith, 1993) and space (e.g. Fairhall & Macaluso, 2009; Graziano & Cooke, 2006;  
8 Graziano, Hu, & Gross, 1997; Spence, 2001). The ability to efficiently integrate multiple  
9 sensory stimuli arising from the same event could be particularly important for painful  
10 sensory stimuli that signal the imminence of a danger threatening the physical integrity of  
11 the body. Pain is typically generated by activation of the nociceptive system, a physiological  
12 system specifically involved in the detection and transmission of information about high  
13 intensity stimuli which have the potential capacity to damage tissue. The mechanisms of  
14 multisensory interactions between somatic and extra-somatic stimuli have been widely  
15 studied with innocuous tactile stimuli, and relatively little with stimuli specifically activating  
16 the nociceptive system. In addition to its importance for understanding the contribution of  
17 multisensory interactions for adaptation to threats, the nociceptive system illustrates  
18 particularly well the challenge for the brain to assess the temporal synchrony of sensory  
19 inputs requiring different times to reach the brain. Indeed, the time taken by a given sensory  
20 input to reach the brain depends on the location at which the eliciting stimulus is received,  
21 i.e. its distance from the brain (e.g. Bergenheim, Johansson, Granlund, & Pedersen, 1996;  
22 Wedel, 2012) and on the conduction velocity with which it is conveyed to the brain (e.g.  
23 Manfron, Filbrich, Nijs, Mouraux, & Legrain, 2020). The nociceptive system mainly consists of  
24 thinly-myelinated A $\delta$  fibers with a conduction velocity of  $\sim 10$ m/s (Kakigi & Shibasaki, 1991)  
25 and unmyelinated C fibers with a conduction velocity of  $\sim 1$ m/s (Opsommer, Masquelier, &  
26 Plaghki, 1999). When applying brief heat stimuli on the hand dorsum, the generated  
27 nociceptive inputs are expected to elicit their first cortical response at about 150 ms for  
28 inputs conveyed by A $\delta$  fibers and at almost 1 s for inputs transmitted by C fibers (Plaghki &  
29 Mouraux, 2005). The more distant the stimulated body part, the greater the delay between  
30 the latencies of A $\delta$ - and C-fiber responses, i.e. smaller when the face is stimulated

31 (Romaniello, Iannetti, Truini, & Cruccu, 2003; Truini, Galeotti, Cruccu, & Garcia-Larrea, 2007)  
32 and greater for the foot (Opsommer et al., 1999). **In contrast, visual inputs reach their first**  
33 **cortical relay in less than 100 ms (Michel, Seeck, & Murray, 2004).** In the case of co-occurring  
34 visual and nociceptive stimuli, visual input will most often reach the brain before the  
35 nociceptive input, and unlike visual input, the latency at which nociceptive input will reach  
36 the brain will depend on the time required for the thermal stimuli to heat the skin, the  
37 transduction time, the length of the peripheral nerve fibers conveying the nociceptive input  
38 to the spinal cord, and the speed at which that input is then transmitted to the cortex.  
39 Considering all these temporal parameters, the binding of concurrent visual and nociceptive  
40 inputs likely requires compensating for the asynchrony of the times at which the different  
41 sensory inputs reach the brain. Such differences in timing between the visual and  
42 nociceptive systems has led to experimental situations in which the onsets of the different  
43 stimuli have been artificially shifted in time to maximize the chances that the stimuli reach  
44 the cortex in the same time-window with the aim of facilitating their mutual interactions  
45 (e.g. Filbrich, Blandiaux, Manfron, Farnè, De Keyser, & Legrain, 2019; Lewald & Guski, 2003)

46 Recently, studies proposed to precisely and individually measure the necessary  
47 asynchrony between nociceptive and visual inputs for them to be perceived as occurring  
48 simultaneously using temporal order judgment (TOJ) tasks (Manfron, Filbrich et al., 2020;  
49 Zampini, Bird, Bentley, Watson, Barrett, Jones, & Spence, 2007). In these tasks, laser-induced  
50 radiant-heat and visual stimuli were administered to participants in pairs, separated by  
51 different time intervals. Participants were asked to judge which of the two stimuli was  
52 perceived first. In Zampini et al.'s study, participants could additionally respond if they  
53 perceived the two stimuli as simultaneous. The point of subjective simultaneity (PSS), i.e.,  
54 the delay between the two stimuli at which the two stimuli have equal chance to be  
55 perceived as occurring first (Manfron, Filbrich et al., 2020; Zampini et al., 2007) or at which  
56 they are judged as occurring simultaneously (Zampini et al., 2007), was measured as  
57 indexing the necessary asynchrony for perceptual simultaneity. In the study of Zampini et al.  
58 (2007), the thermo-nociceptive stimuli were applied on the forearm with a thermal energy  
59 activating A $\delta$  fibers and the visual stimuli were projected onto the same skin area. The mean  
60 PSS value was estimated at ~40 ms (under a condition during which participants' attention  
61 was equally shared between the nociceptive and visual stimuli). More precisely, the

62 nociceptive stimulus transmitted through A $\delta$  fibers needed to precede the visual stimulus by  
63 40 ms on average in order for both stimuli to be perceived at the same time. Using a similar  
64 paradigm with nociceptive stimuli applied on the hand dorsum, Manfron, Filbrich et al.  
65 (2020) estimated such a delay at ~76 ms. In the latter study, lower laser thermal energies  
66 were also applied to selectively activate ultra-slow C fibers having a lower thermal activation  
67 threshold than A $\delta$ -fiber nociceptors. Thermal stimuli mediated by C fibers had to precede  
68 visual stimuli by ~577 ms on average to achieve perception of simultaneity, evidencing that  
69 the asynchrony is dependent on the type of thermo-nociceptive fibers that are stimulated.

70 In these two studies, nociceptive and visual stimuli were always applied in close spatial  
71 proximity to each other, that is, the visual stimulus was projected onto or presented near  
72 the skin area on which the nociceptive stimulus was applied. Spatial congruence between  
73 sensory stimuli was found to be a key feature in determining multisensory interactions (e.g.  
74 Brozzoli, Ehrsson, & Farnè, 2014; di Pellegrino & Làdavas, 2015; Farnè, Demattè, & Làdavas,  
75 2005; Fujisaki, Kitazawa, & Nishida, 2012; Macaluso & Maravita, 2010; Serino, 2019; Stein &  
76 Meredith, 1993). Interactions between somatic (e.g. tactile, nociceptive) and extra-somatic  
77 (e.g. visual, auditory) stimuli are particularly enhanced when the extra-somatic stimuli occur  
78 within the peripersonal space of the body, defined as a representation of the body slightly  
79 extending in the space adjacent to the stimulated limb (e.g. De Paepe, Crombez, & Legrain,  
80 2017; di Pellegrino & Làdavas, 2015; Filbrich, Alamia, Blandiaux, Burns, & Legrain, 2017;  
81 Filbrich, Halicka, Alamia, & Legrain, 2018; Legrain & Torta, 2015; Serino, 2019). The  
82 peripersonal space plays a critical role in the processing of threatening stimuli as it  
83 represents the area of external space where objects can have an immediate impact on body  
84 integrity (Graziano & Cooke, 2006; Legrain & Torta, 2015). Accordingly, it has been  
85 repeatedly shown that interactions between visual and nociceptive stimuli, i.e. their capacity  
86 to modify the perception of each other, are greatest when the visual stimuli are approaching  
87 or presented near the bodily area on which the nociceptive stimuli are applied (De Paepe,  
88 Crombez, & Legrain, 2015; De Paepe et al., 2017; De Paepe, Crombez, Spence, & Legrain,  
89 2014; De Paepe, Crombez, & Legrain, 2016; Filbrich, Alamia, Blandiaux, et al., 2017; Filbrich  
90 et al., 2019; Filbrich et al., 2018; Manfron, Legrain, & Filbrich, 2020; Vanderclausen, Filbrich,  
91 Alamia, & Legrain, 2017). Therefore, it might reasonably be assumed that the necessary time  
92 delay between nociceptive and visual stimuli for them to be perceived as occurring

93 simultaneously depends on whether they are spatially congruent or not. For instance,  
94 studies having used TOJ or simultaneity judgment tasks between visual and tactile (Spence,  
95 Baddeley, Zampini, James, & Shore, 2003; Spence, Shore, & Klein, 2001) or between visual  
96 and auditory stimuli (Spence et al., 2003; Zampini, Guest, Shore, & Spence, 2005; Zampini,  
97 Shore, & Spence, 2003a; Zampini, Shore, & Spence, 2003b) showed that PSS values were  
98 smaller when two different sensory stimuli were presented within the same spatial area, as  
99 compared to when they were presented at different locations. This suggests that when the  
100 two different inputs were closer in space, their interaction increased, leading to smaller time  
101 intervals between the inputs for them to be perceived at the same time. In addition, authors  
102 observed greater just-noticeable differences (JND) when the two stimuli were closer  
103 together (provided, however, that stimuli were presented laterally to either side of the body  
104 midline [Zampini et al., 2003b]). Derived from the slope of the psychometric functions used  
105 to fit participants' judgements, the JND corresponds to the minimum amount of time  
106 necessary between the two stimuli to perceive their order accurately. The flattening of the  
107 slope, and therefore an increase of the JND, would index a lower precision in the ability to  
108 discriminate the temporal order between the two stimuli when they are close together. This  
109 would suggest that spatial proximity facilitated the interaction between the stimuli of the  
110 different sensory modalities, as if they arose from a single sensory event, and, consequently,  
111 made them difficult to be perceived as distinct stimuli despite the instruction to report the  
112 temporal order between two stimuli (Spence et al., 2003; Spence et al., 2001; Zampini et al.,  
113 2003a; however, see Zampini et al., 2003b for an alternative explanation).

114 In addition to the distance of the peripheral receptors and the conduction speed of the  
115 nociceptive inputs, **the aforementioned data** suggest that the proximity of the visual  
116 stimulus relative to the body area on which the nociceptive stimuli are applied also  
117 influences the perceived asynchrony between visual and nociceptive inputs. Although the  
118 temporal and spatial aspects of the different sensory inputs are closely related during  
119 multisensory interactions, they have mostly been studied separately. Considering them  
120 jointly, especially during visuo-nociceptive interactions, is relevant to understand how  
121 humans can efficiently detect and react to potentially harmful sensory events. The present  
122 experiment investigated whether the amount of time by which the nociceptive stimulus  
123 must precede the visual stimulus for them to be perceived as presented first equally often

124 depends on the spatial proximity between the two stimuli. We first predicted that spatial  
125 congruence between nociceptive and visual stimuli presented in pairs would decrease the  
126 PSS between the two stimuli. It is indeed hypothesized that two sensory inputs occurring in  
127 the same spatial area would allow the brain to compensate for their different times of  
128 arrival. In addition, based on the results of previous experiments (Spence et al., 2003;  
129 Spence et al., 2001; Zampini et al., 2003a), we expected order judgments to be less precise  
130 when the stimuli were spatially congruent. To these aims, we applied brief laser-induced  
131 thermal stimuli on participants' hand dorsa with an energy eliciting responses mediated by  
132 either A $\delta$  fibers or C fibers, in order to generate thermo-nociceptive inputs transmitted with  
133 different conduction velocities. The visual stimuli were delivered by means of a white light-  
134 emitting diode placed either next to the hand onto which the laser stimuli were applied or  
135 next to the opposite non-stimulated hand.

136

## 137 **2. Methods**

### 138 *2.1. Participants*

139 Thirty-seven volunteers participated in the study, randomly assigned to one of two  
140 groups. The number of participants in each group was based on previous studies having used  
141 similar experimental paradigms (e.g. Filbrich, Alamia, Blandiaux, et al., 2017; Filbrich, Alamia,  
142 Burns, & Legrain, 2017; Filbrich et al., 2018; Manfron, Filbrich et al., 2020). Exclusion criteria  
143 were non-corrected vision difficulties, any severe neurological or psychiatric diseases,  
144 cardiac problems, chronic pain disorders, trauma of the upper limbs within the last 6  
145 months preceding the experiment, tissue damage or dermatological disease of the hands,  
146 regular use of psychotropic drugs, and intake of analgesic drugs (e.g., NSAIDs and  
147 paracetamol) within the 12 hours before the experiment. Having participated in the  
148 experiments of our previous study (Manfron, Filbrich et al., 2020) was also considered as an  
149 exclusion criterion. The data of five participants were excluded from the analyses because of  
150 technical failures (see data analyses section). The mean age of the remaining 32 participants  
151 (19 women, 13 men) was 22.81 years ( $SD = \pm 3.22$ , range 18-30). According to the Flinders  
152 Handedness Survey (Nicholls, Thomas, Loetscher, & Grimshaw, 2013), 28 participants were

153 right-handed and 4 left-handed. The local ethic committee (Comité d'Éthique hospitalo-  
154 facultaire, Saint-Luc University Hospital & UCLouvain) approved the experimental procedure  
155 in agreement with the Declaration of Helsinki. All volunteers signed an informed consent  
156 prior to the experiment and received financial compensation for their participation.

157

## 158 2.2. *Stimuli and apparatus*

159 Visual stimuli consisted of 5-ms flashes delivered by means of a white light-emitting diode  
160 (LED) with a 17-lm luminous flux, a 6.40-cd luminous intensity, and a 120° diffusion angle  
161 (GM5BW97330A, Sharp Corporation, Japan).

162 Thermo-nociceptive stimuli consisted of radiant heat stimuli applied on one of the hand  
163 dorsa using a temperature-controlled CO<sub>2</sub> laser stimulator (10,6 μm wavelength, Laser  
164 Stimulation Device, SIFEC, Ferrières, Belgium). The laser beam was conveyed through a 10-m  
165 optical fiber ending with a head containing the optics used to collimate the laser beam to 6  
166 mm diameter at the target site. The laser head was held upon the participant's hand by  
167 means of an articulated arm attached to a camera tripod system (Manfrotto, Cassola, Italy).  
168 The laser head was fixed into a clamp attached to a 3-way head, allowing displacements of  
169 the laser target perpendicularly to the hand's dorsum by means of two sliders in all  
170 directions. A laser stimulus lasted 100 ms with a 10-ms heating ramp to reach the target  
171 temperature, followed by a 90-ms plateau; heating was then stopped. Laser energy was  
172 controlled in temperature measured at the skin target site by means of a radiometer in the  
173 laser head. The laser output power was thus adapted to the online measurement of the skin  
174 temperature at the site of stimulation, to reach the specified temperature. The target  
175 temperature was individually determined according to the activation threshold of  
176 unmyelinated C fibers and thinly myelinated Aδ fibers, respectively. Thresholds were  
177 estimated using an adaptive staircase procedure. The absolute detection threshold was used  
178 to determine detections triggered by C-fiber inputs, and reaction times (RTs) to determine  
179 detections triggered by Aδ-fiber inputs. These two different procedures are based on the  
180 differences in physiological properties of Aδ and C fibers, namely that C fibers have a lower  
181 activation threshold than Aδ fibers and that Aδ fibers have a faster conduction velocity than  
182 C fibers (for details, see Churyukanov, Plaghki, Legrain, & Mouraux, 2012). Threshold



183 assessments were done separately for each hand. To measure C-fiber activation threshold,  
184 series of laser stimuli were delivered with a starting temperature of 39°C and participants  
185 were asked to respond whether they felt or not the sensation elicited by each stimulus.  
186 When the stimulus was not reported, the temperature of the stimulus of the next trial was  
187 incremented by 0.5°C. When it was reported, the temperature was decreased by 0.5°C. The  
188 procedure lasted until four reversals were encountered. The average of the four  
189 temperatures that led to a reversal was considered as the activation threshold of C fibers. To  
190 measure A $\delta$ -fiber activation threshold, a similar procedure was used except that RTs were  
191 used as adaptive criterion. As the conduction velocity of A $\delta$  fibers is faster than that of C  
192 fibers (Plaghki & Mouraux, 2005), it has been shown that a cut-off of 650 ms effectively  
193 discriminates the responses elicited by the activity of A $\delta$  fibers and C fibers respectively,  
194 during stimulation of the hand dorsum (Churyukanov et al., 2012). The participants were  
195 thus required to press a button as fast as possible when they felt the stimulus. They held the  
196 button in the hand opposite to the one on which laser stimuli were applied. The first  
197 stimulus was delivered with a temperature of 46°C. When RTs were greater than or equal to  
198 650 ms, the temperature of the stimulus of the next trial was increased by 0.5°C. When RTs  
199 were smaller than 650 ms (indicating a detection mediated by A $\delta$  fibers), the temperature  
200 was decreased by 0.5°C. After four reversals, the procedure was stopped and the average of  
201 the four temperatures that led to a reversal was considered as the activation threshold of A $\delta$   
202 fibers.

203 Individual detection thresholds were used to determine, for each participant, the target  
204 temperature of the stimuli used during the TOJ task. To avoid overheating of participants'  
205 hands and habituation, only one type of fiber was tested for each participant. Half of the  
206 participants were presented stimuli activating only C fibers, while participants of the other  
207 group were presented stimuli eliciting sensations compatible with the activation of A $\delta$  fibers.  
208 For each participant of the C-fiber group, the two threshold measurement procedures  
209 described above were applied, and the estimated threshold values for C and A $\delta$  fibers were  
210 averaged to obtain the target temperature value. At such intensity, stimuli were expected to  
211 activate C-fiber afferents without concomitantly activating A $\delta$ -fiber afferents. For each  
212 participant of the A $\delta$ -fiber group, only the procedure to determine the A $\delta$ -fiber activation  
213 threshold was used, and the experimental target temperature was set 5°C above the A $\delta$ -

214 fiber activation threshold to ensure the stimulation of A $\delta$  fibers without producing any burn  
215 lesions (for details, see Lenoir, Algoet, et al., 2018). Participants were asked to qualify the  
216 elicited sensation using a list of descriptor words (see Nahra & Plaghki, 2003) to ensure that  
217 it was compatible with the activation of the target fiber. Accordingly, participants of the C-  
218 fiber group qualified the sensation elicited by stimuli of the target temperature as warm,  
219 while participants of the A $\delta$ -fiber group qualified the sensation as pricking.

220

### 221 2.3. Procedure

222 During the experiment, participants sat on a chair in front of a table in a lighted room. A  
223 fixation cross was located on the table surface, aligned with their midsagittal plane, pasted  
224 at 40 cm from their trunk. They were asked to place their hands palms down on the table,  
225 with the metacarpophalangeal joint between each index finger and the thumb located 1 cm  
226 from two landmarks. The landmarks were separated by 30 cm from each other along a line  
227 perpendicular to participants' midsagittal plane, at 30 cm from their trunk. At equal distance  
228 from each landmark (~18 cm), 10 cm above the perpendicular line, participants gazed at the  
229 central fixation cross. The white LED was pasted on one of the two landmarks according to  
230 the tested condition and the experimental blocks (see Fig. 1).

231 The TOJ task consisted of four blocks of 40 trials each. A trial consisted of a pair of one  
232 visual stimulus and one laser stimulus delivered at the target temperature determined  
233 according to the group to which participants had been assigned (i.e., eliciting sensation  
234 compatible with either C-fiber or A $\delta$ -fiber activation). Before the task, two pairs of stimuli  
235 were administered to all participants to get familiarized with the task and the sensation  
236 elicited by the activation of the specific fibers. Their performance was not recorded. During  
237 the task, the laser stimuli were applied on the left hand during two blocks, and on the right  
238 hand during the two other blocks (see below). For each hand, the trials of one block were  
239 delivered with the visual stimulus presented next to the hand receiving the laser stimulus  
240 (ipsilateral condition). During the other block, the visual stimulus was presented next to the  
241 opposite hand, i.e., the non-stimulated hand (contralateral condition; Fig. 1). Since the *psi*  
242 adaptive procedure was used and 40 trials were necessary to estimate the parameters of  
243 interest (see Measures section), the main variable (i.e., visual stimulus ispi- vs. contralateral

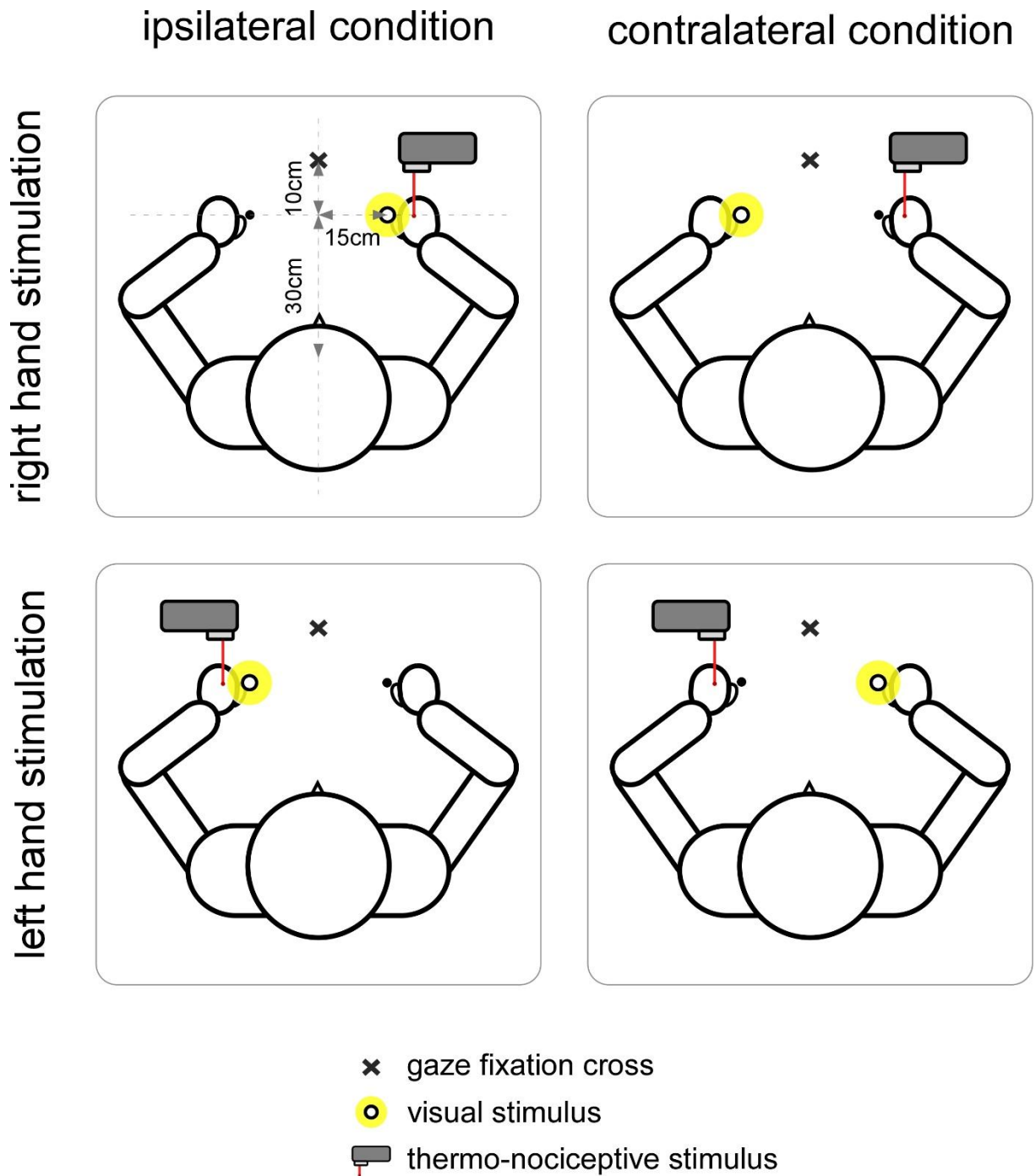
244 to the stimulated hand) was manipulated in a block-design instead of mixing it in the same  
245 block.

246 A trial started with a warning signal from the experimenter. Approximately 500 ms later,  
247 the first stimulus of the visuo-nociceptive pair was delivered, followed by the second  
248 stimulus according to different stimulus onset asynchronies (SOAs). For the C-fiber group,  
249 stimuli were separated by 16 possible SOAs: +100, +220, +270, +320, +370, +420, +460,  
250 +490, +510, +540, +580, +630, +680, +730, +780, +900 ms. For the A $\delta$ -fiber group, there  
251 were 14 possible SOAs:  $\pm$ 200,  $\pm$ 150,  $\pm$ 100,  $\pm$ 80,  $\pm$ 60,  $\pm$ 40,  $\pm$ 20 ms. Positive values indicate  
252 that the laser stimulus was applied before the visual stimulus, negative values indicate that  
253 the visual stimulus was presented before the laser stimulus. The laser stimulus always  
254 preceded the visual stimulus in the C-fiber group, because of the very late latency of  
255 responses to C-fiber stimuli. Also, the number of possible SOAs was larger in that group  
256 because of the larger variability of the responses during trials with C-fiber stimuli, as  
257 compared to trials with A $\delta$ -fiber stimuli (see Manfron, Filbrich et al., 2020). The to-be-  
258 presented SOA was determined at each trial using the adaptive *psi* method considering the  
259 participant's responses to all previous trials of the block (Kingdom & Prins, 2010). Based on a  
260 Bayesian framework, this adaptive procedure estimates the posterior distribution of the  
261 parameters of interest by minimizing their expected entropy (i.e., uncertainty) trial by trial,  
262 so that the SOA selected at each trial gives the most information to estimate the parameters  
263 of interest without probing extensively all the possible SOAs (for further details about the  
264 use of the *psi* method in the context of TOJ tasks, see Filbrich, Alamia, Burns, & Legrain,  
265 2017).

266 For each trial, participants were asked to judge which of the visual or the thermo-  
267 nociceptive stimulus they perceived as occurring first during two blocks, one for each spatial  
268 congruence condition (i.e., visual stimulus ipsilateral vs. contralateral to the hand receiving  
269 the laser stimulus). During the two other blocks, they were asked to report which stimulus of  
270 the pair was perceived as second. Using both "*which is first*" and "*which is second*"  
271 responses was intended to dissociate genuine changes in the perceived temporal order from  
272 potential response/decisional biases (see Shore, Spence, & Klein, 2001; Filbrich, Torta,  
273 Vanderclausen, Azañón, & Legrain, 2016 for a detailed description and discussion). Within  
274 each of the two groups, half of the participants of each group responded to "*which is first*"

275 with the laser stimuli applied to the left hand and to “*which is second*” with the laser stimuli  
276 applied to the right hand. The reverse was done for the other half of participants. Judgments  
277 were reported verbally, with no speed requirement, by using the words ‘*visual*’ or ‘*laser*’.  
278 The order of the four blocks was counterbalanced for each participant. Once the  
279 experimenter encoded the participants’ response (by pressing a key of the remote-control  
280 computer), the next trial started 2000 ms later. The laser beam was displaced after every  
281 trial to avoid habituation and skin overheating.

282 To check that the used temperatures elicited appropriate sensations related to C fibers or  
283 A $\delta$  fibers respectively, participants qualified after each trial their perception using a list of  
284 descriptor words (Nahra & Plaghki, 2003). A trial was discarded and repeated if the laser  
285 stimulus was not perceived, if the C-fiber laser stimulus was qualified as pricking, or if the  
286 A $\delta$ -fiber laser stimulus was qualified as warm. Each block lasted approximately 5 minutes.  
287 After each block, there was a short break period during which the LED was displaced to the  
288 landmark next to the other hand. The entire experiment, including instructions and  
289 threshold measurements, lasted about 1 hour and a quarter.



291

292 **Figure 1. Design of the experiment.** Participants performed temporal order judgments on  
 293 pairs of thermo-nociceptive (CO<sub>2</sub> laser illustrated by the red laser beam) and visual stimuli  
 294 (light-emitting diode, illustrated by the white circle with yellow halo when on, and black dot  
 295 when off), while staring at the fixation cross. Participants were seated on a chair, palms'  
 296 down on a table at ~30cm from the trunk, 15 cm on either side of the fixation cross. One  
 297 group received thermo-nociceptive stimuli eliciting responses of C fibers whereas the other  
 298 group received nociceptive stimuli eliciting A $\delta$ -fiber responses. Laser stimuli were applied on

299 either the left or the right hand depending on the stimulation blocks. Across blocks, the  
300 visual stimulus was presented either next to the stimulated hand (ipsilateral condition), or  
301 next to the opposite non-stimulated hand (contralateral condition).

302

303        2.4.        *Measures*

304        Activation threshold and target temperature values of laser stimuli were measured in  
305        degrees Celsius.

306        To estimate TOJ performance, the proportion of thermo-nociceptive stimuli perceived as  
307        being presented first was computed as a function of the SOAs for each experimental  
308        condition. TOJ parameters were estimated by a logistic function  $f(x)=1/(1+exp(-\beta(x-\alpha)))$  at  
309        each trial (Kingdom & Prins, 2010). Analyses were made on the last estimates of the block,  
310        corresponding to the last update of the adaptive procedure. The main parameter of interest  
311        was the  $\alpha$  value, corresponding to the threshold of the function which characterizes the  
312        point of subjective simultaneity (PSS), that is, the SOA at which the thermo-nociceptive  
313        stimulus and the visual stimulus are perceived as occurring first equally often (i.e., the 0.5  
314        criterion on the ordinate; Fig. 2). Accordingly, the PSS was used as a measure of the amount  
315        of time that was needed between the thermo-nociceptive stimulus and the visual stimulus  
316        to have equal chance to be perceived as occurring first, indexing the asynchrony at which  
317        they were perceived at the same time (Spence et al., 2001). Based on Manfron, Filbrich et al.  
318        (2020), its prior estimates were set to  $500\pm 200$  ms for the C-fiber group and  $70\pm 20$  ms for  
319        the A $\delta$ -fiber group. The  $\beta$  value was analyzed as second parameter of interest. It corresponds  
320        to the slope of the psychometric curve and describes the noisiness of the results, i.e., the  
321        variability of participants' responses during the experiment (Kingdom & Prins, 2010). Lower  
322        and higher abilities to discriminate the temporal order of the two stimuli is represented by  
323        lower and greater values of  $\beta$ , respectively. Its prior estimates were set to  $0.06 \pm 0.6$  for both  
324        fiber groups.

325

326        2.5.        *Data analyses*

327        Five participants were discarded from the analyses due to technical failures and/or  
328        excessive habituation that affected participants' ability to perceive the laser stimuli  
329        throughout the experiment, resulting in high variability in their responses during the TOJ  
330        task, as evidenced by flat psychometric slopes. Statistical analyses were conducted with IBM  
331        SPSS 23. First, we tested whether activation threshold and target temperature values were  
332        similar between the two hands by using paired sample t tests for each fiber group. Next,

333 before analyzing TOJ data, data from the two response modes (“*which is first?*” vs. “*which is*  
334 *second?*”), and therefore those of the left-hand and right-hand stimulation blocks, were  
335 averaged for each spatial congruence condition (ipsilateral vs contralateral) and each group  
336 (A $\delta$  fibers vs C fibers). Therefore, the *response mode* and *stimulated hand* variables were  
337 disregarded from analyses. Resulting PSS and slope values were then compared using  
338 analyses of variance (ANOVAs) for repeated measures with the spatial congruence as within-  
339 subject factor (ipsilateral vs. contralateral) and the group as between-subjects factor (C-fiber  
340 vs. A $\delta$ -fiber). Effect sizes were measured by means of partial Eta squared for ANOVAs and  
341 Cohen’s d for t tests. If necessary, contrast analyses were performed. Significance level was  
342 set at  $p$ -value < 0.05. Data are expressed in means plus or minus standard deviation (M $\pm$ SD).

### 343 3. Results

#### 344 1.1. Activation threshold and target temperature values

345 Comparisons of the threshold values between the two hands did not reveal any  
346 significant difference, for none of the groups (*C-fiber*: left hand= 39.9 $\pm$ 1.31 $^{\circ}$ C; right hand=  
347 39.8 $\pm$ 1.67 $^{\circ}$ C,  $t(15) = 0.47$ ,  $p = 0.642$ ,  $d = 0.12$  ; *A $\delta$ -fiber*: left hand= 47.5 $\pm$ 2.00 $^{\circ}$ C, right hand=  
348 47.9 $\pm$ 2.36  $^{\circ}$ C;  $t(15)= -0.99$ ,  $p = 0.337$ ,  $d = -0.25$ ). These values are in the range of the  
349 temperatures usually associated with C-fiber and A $\delta$ -fiber afferent activation respectively  
350 (Churyukanov et al., 2012; Plaghki et al., 2010). Consequently, the target temperature values  
351 used during the experiment were not different between the left and the right hands for both  
352 the C-fiber group (left hand: 44.25 $\pm$ 1.24 $^{\circ}$ C; right hand: 44.50 $\pm$ 1.63 $^{\circ}$ C;  $t(15) = -0.89$ ,  $p = 0.388$ ,  
353  $d = -0.22$ ) and the A $\delta$ -fiber group (left hand: 52.31 $\pm$ 2.02  $^{\circ}$ C; right hand: 52.69 $\pm$ 1.89  $^{\circ}$ C;  $t(15)=$   
354  $-1.695$ ,  $p = 0.111$ ,  $d = -0.42$ ).

355

#### 356 1.2. TOJ values

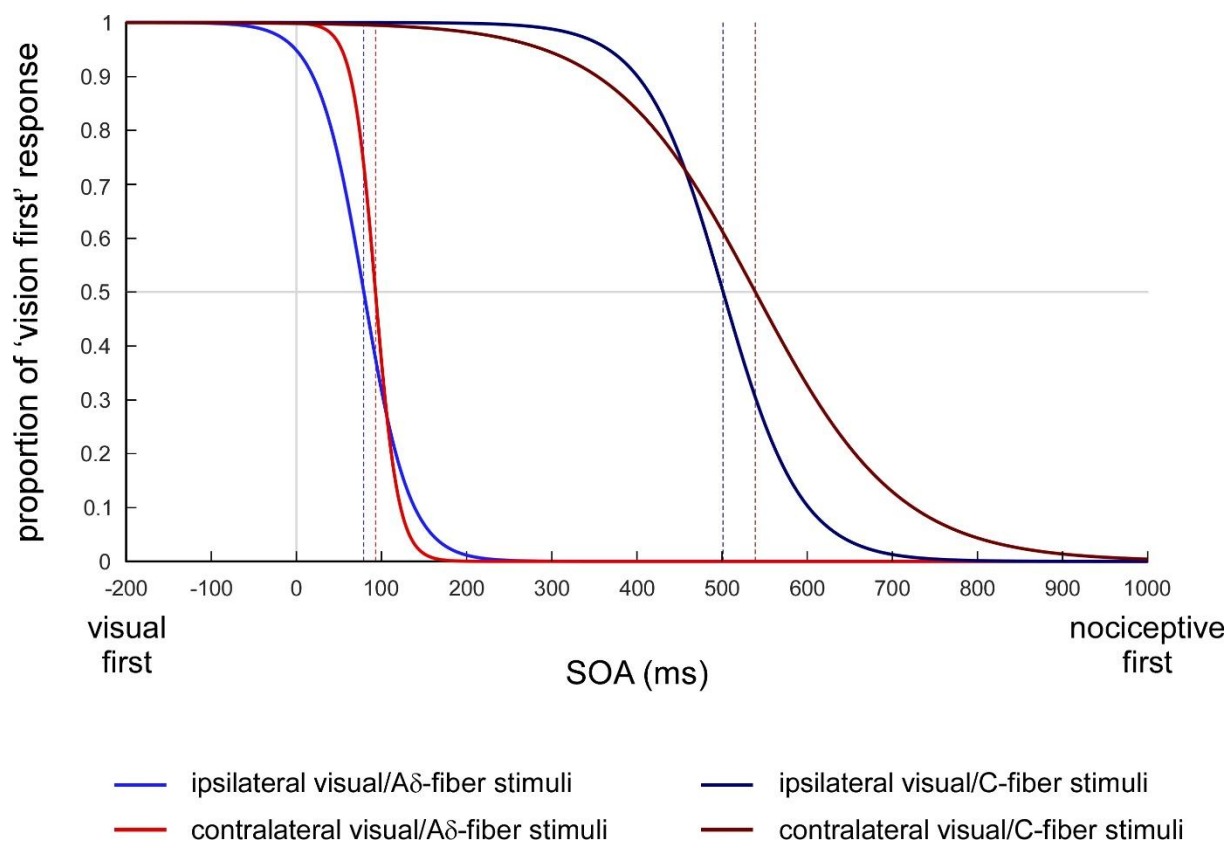
357 The ANOVA performed on the PSS values showed a significant main effect of the group  
358 factor ( $F(1,30) = 240.17$ ,  $p < 0.001$ ,  $\eta^2_p = 0.89$ ), confirming that PSS between visual and  
359 thermo-nociceptive stimuli was dependent on the type of stimulated thermo-nociceptive  
360 fiber. The ANOVA also revealed a significant main effect of *spatial congruence* ( $F(1,30) =$



361 10.65,  $p = 0.003$ ,  $\eta^2_p = 0.262$ ), with no significant interaction with the *group* factor ( $F(1,30) =$   
362 2.337,  $p = 0.137$ ,  $\eta^2_p = 0.072$ ). This suggests that the location of the visual stimulus relative to  
363 the hand receiving the thermo-nociceptive stimuli affected the PSS in a similar fashion for  
364 the two subtypes of applied thermo-nociceptive stimuli (see Figs. 2 and 3). When C fibers  
365 were stimulated, PSS values were ~40 ms greater when the visual stimulus was presented  
366 contralaterally to the stimulated hand, as compared to when it was presented ipsilaterally  
367 (ipsilateral: 501±121ms; contralateral: 539±108 ms). This difference was ~12 ms when A $\delta$   
368 fibers were stimulated (ipsilateral: 79±13 ms; contralateral: 92±18 ms).

369 Regarding the slope values, the data of one participant in the C-fiber group was removed  
370 from the analyses because the slope value of the ipsilateral condition was identified as an  
371 outlier as compared to the group mean. The ANOVA revealed a significant main effect of  
372 *group* ( $F(1,29)=11.56$ ,  $p = 0.002$ ,  $\eta^2_p = 0.28$ ) with higher slope values for the A $\delta$ -fiber group  
373 (0.055) than for the C-fiber group (0.012). No significant main effect of *spatial congruence*  
374 emerged from the analyses ( $F(1,29) = 3.211$ ,  $p = 0.084$ ,  $\eta^2_p = 0.10$ ) nor any significant  
375 interaction between both factors ( $F(1,29)= 3.264$ ,  $p = 0.081$ ,  $\eta^2_p = 0.10$ ) (see Fig. 2 and 3).

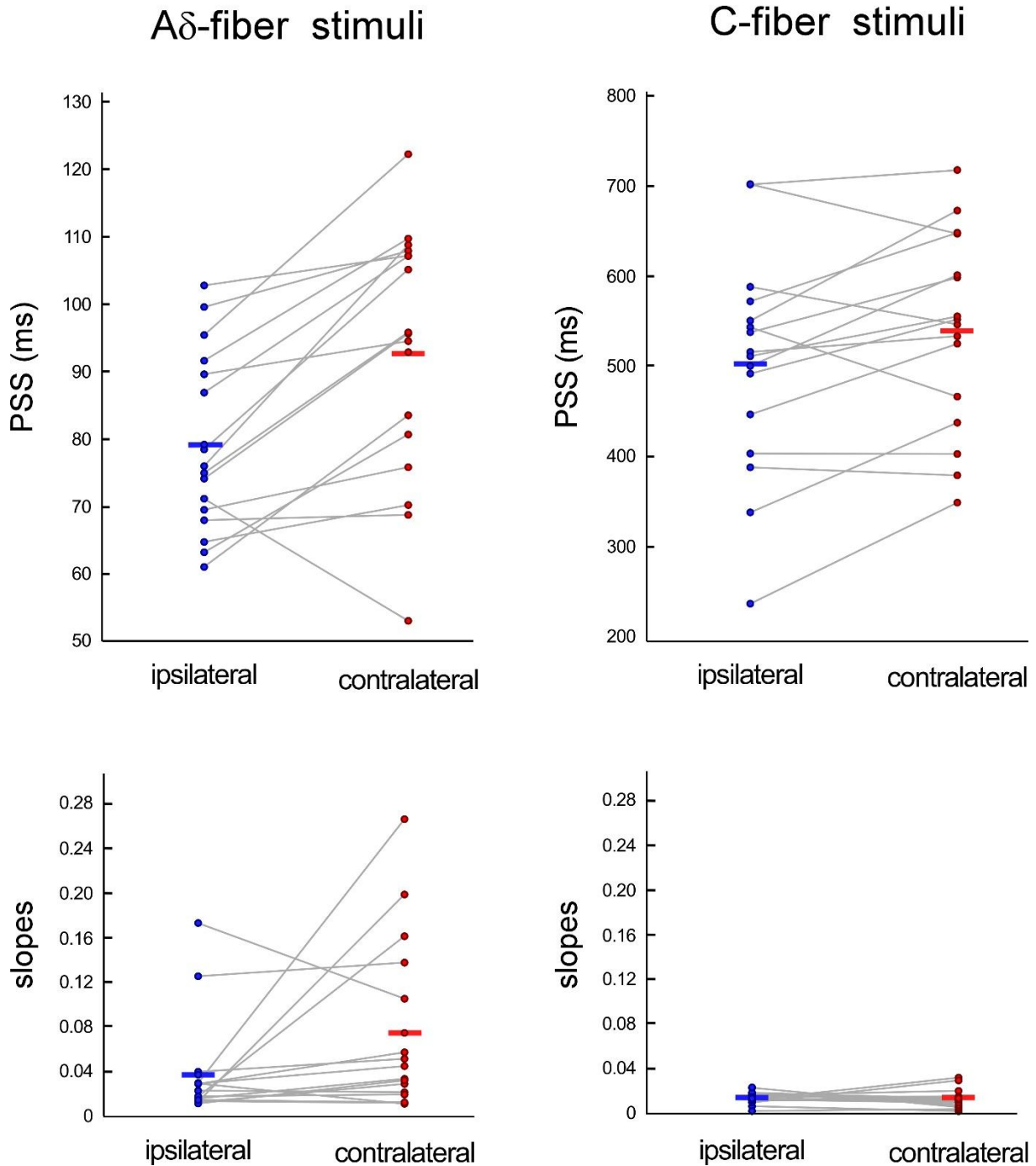
376



**Figure 2. Logistic functions fitting participants performances.** The graph illustrates the averaged results for the 16 participants of each group. The left curves correspond to the fitted logistic functions for the group of participants having received thermal stimuli eliciting responses mediated by A $\delta$  fibers, with the light blue curve representing the condition in which the visual stimulus was presented on the side of space ipsilateral to the hand on which the thermo-nociceptive stimulus is applied and the light red curve the condition in which the visual stimulus was presented on the side of space contralateral to the hand on which the thermo-nociceptive stimulus is applied. The right curves correspond to the fitted logistic functions for group of participants having received thermal stimuli activating selectively C fibers, with the dark blue curve representing the ipsilateral condition and the dark red curve the contralateral condition. The x-axis represents different hypothetical stimulus onset asynchronies (SOAs) between the visual and the thermo-nociceptive stimuli: negative values indicate that the visual stimulus was presented first, while positive values indicate that the nociceptive stimulus was presented first. The y-axis represents the proportion of trials in which the participants perceived the visual stimulus as first presented. In both groups, the visual stimulus always needed to be administered after the nociceptive stimulus, but, most

394 importantly, the point of subjective simultaneity of the contralateral condition was larger  
395 than the PSS of the ipsilateral condition, for both types of thermo-nociceptive fibers.

396



397

398

399 **Figure 3. Individual PSS and slope values per group.** The figure shows scatter plots displaying  
400 individual PSS values (on the top) and individual slope values (on the bottom), represented by  
401 the black dots, for each group (A $\delta$  vs C-fiber) according to the visual condition (ipsilateral vs

402 contralateral). The black strips show the means of each parameter. Data of the same  
403 participant are linked by a light grey line.

404

406 Efficient multisensory interactions notably depend on the temporal co-occurrence  
407 between stimuli belonging to different sensory modalities (e.g. Macaluso et al., 2016;  
408 Meredith, Nemitz, & Stein, 1987; Morein-Zamir, Soto-Faraco, & Kingstone, 2003; Spence &  
409 Squire, 2003; Stein & Meredith, 1993; Sugita & Suzuki, 2003). It is however a challenge for  
410 the brain to integrate sensory inputs triggered by a given event but arriving at cortical level  
411 with different delays (Colonius & Diederich, 2004; Fujisaki, Kitazawa, & Nishida, 2012;  
412 Meredith et al., 1987; Spence & Squire, 2003) because of differences in transduction and/or  
413 conduction times. Moreover, in the case of somatic stimuli, peripheral conduction distances  
414 and hence peripheral conduction times depend greatly on where the stimuli occur on the  
415 body (e.g., Plaghki & Mouraux, 2005, Cruccu et al., 2008). This is most striking for nociceptive  
416 input conveyed by unmyelinated C fibers because of their very slow conduction velocity.  
417 Studies have investigated the factors influencing perceptual asynchrony during interactions  
418 between visual-auditory, visual-tactile and visual-nociceptive modalities by measuring the  
419 ability of participants to perceive the temporal order between the stimuli of the tested  
420 modalities (Manfron, Filbrich et al., 2020; Spence et al., 2001; Spence et al., 2003; Zampini  
421 et al., 2003a; Zampini et al., 2005; Zampini et al., 2007).

422 The present study investigated whether the ability to perceive the temporal order  
423 between visual and nociceptive stimuli was also dependent on the spatial proximity between  
424 the location of the visual stimulus and the body area on which the thermo-nociceptive  
425 stimulus was applied. In line with previous studies that investigated visual-auditory (Spence  
426 et al., 2003; Zampini, Guest, et al., 2005; Zampini et al., 2003a) and visual-tactile interactions  
427 (Spence et al., 2003; Spence et al., 2001), the results showed that the PSS between visual  
428 and thermo-nociceptive stimuli was significantly smaller when the two stimuli were close  
429 together, i.e. when the visual stimulus was applied near the stimulated hand as compared to  
430 when it was applied near the opposite hand. This was observed regardless of whether the  
431 nociceptive inputs were conveyed by A $\delta$  or C fibers. This indicates perceptual simultaneity  
432 with smaller asynchrony between visual and nociceptive stimuli when they are close  
433 together than when they are far from each other. These results are in agreement with those  
434 of other studies having recurrently shown that visual stimuli and nociceptive stimuli mostly

435 conveyed by A $\delta$  fibers optimally interact when the visual stimuli are presented in the close  
436 vicinity of the limb on which the nociceptive stimuli are applied, whatever the position of the  
437 stimulated limb in external space and the visual field in which the visual stimuli appear (De  
438 Paepe et al., 2014, 2015, 2017; Filbrich, Alamia, Blandiaux, et al., 2017; Filbrich et al., 2018;  
439 Vanderclausen et al., 2017).

440 Two non-exclusive mechanisms could potentially explain the effect of spatial congruence  
441 on the perception of simultaneity between sensory inputs transmitted through different  
442 modality pathways: crossmodal attention and multisensory integration. First, according to  
443 the attention-switching hypothesis, when task stimuli are not located next to each other,  
444 participant's attention must be shifted from the location of the first stimulus of the pair  
445 toward the location of the second stimulus to correctly judge their temporal order (Spence,  
446 2001; Zampini et al., 2003a). In other words, the greater PSS values observed in the  
447 contralateral condition would reflect the cost of shifting attention from one location to  
448 another. On the contrary, in the ipsilateral condition, as participants only focus their  
449 attention on one single location to meet the requirements of the task, interactions between  
450 the ipsilateral stimuli would be improved, as compared to the contralateral condition,  
451 leading to smaller PSS values. Additionally, in accordance with the prior-entry effect (e.g.  
452 Spence, 2001; Spence & Parise, 2010; Titchener, 1908; Filbrich, Alamia, Burn, & Legrain,  
453 2017), it could also be that the first stimulus of the pair has actually attracted attention to its  
454 own location, having facilitated the processing and the perception of the second stimulus  
455 when it occurred at the same location, as compared to when it appeared in the opposite  
456 side of space.

457 Second, according to the multisensory integration hypothesis, presenting two sensory  
458 stimuli simultaneously – or at least within the same time-window – at the same location  
459 increases the likelihood to bind them together and perceive them as one unique and  
460 coherent sensory event, as compared to when they are presented in different locations (e.g.  
461 Spence, 2001; Spence & Squire, 2003; Stein & Meredith, 1993; Welch, 1999; however, see  
462 also Spence, 2013 for a different account). In the context of TOJ tasks, the tendency of  
463 merging the stimuli into a single integrated percept would speed up their processing. This  
464 integration would seem relatively automatic given that, by judging the temporal order of the  
465 two stimuli, participants are explicitly asked to perceive them as two distinct sensory events

466 in those tasks. In turn, the disadvantage of integrating the two stimuli would also make it  
467 difficult to dissociate them as two distinct events, decreasing the precision of their temporal  
468 order judgments. On the contrary, presenting the stimuli at distinct locations would increase  
469 their discriminability and lead to better performances. This was indeed shown in previous  
470 TOJ studies by higher just-noticeable difference (JND) values – and therefore flatter slope  
471 values – when the two stimuli were presented at the same location, as compared to when  
472 they were presented at distinct locations (Spence et al., 2003; Spence et al., 2001; Zampini  
473 et al., 2003a). However, in the present study, no significant differences were observed for  
474 the slope values between the conditions during which visual and nociceptive stimuli were  
475 presented at the same location and those during which they were presented at opposite  
476 locations. This suggests that the precision of the participants' judgments was not affected by  
477 the spatial congruence between the two stimuli. The method we used in the present study is  
478 however quite different from the one used in previous experiments (Spence et al., 2003;  
479 Spence et al., 2001; Zampini et al., 2003a). We used an adaptive procedure to present the  
480 different time-interval conditions, and the last estimate of the slope was used to index  
481 participants' performances. In previous studies, fixed time intervals were presented with a  
482 constant stimulation procedure, and the JND was derived from the probability of 75% of  
483 perceiving the temporal order of the stimuli correctly. The use of different methods is  
484 nevertheless unlikely to explain the differences between the results of present vs. previous  
485 studies. Indeed, the different estimates of the slope values of the TOJ functions seem usually  
486 similarly sensitive to the same factors, whatever the procedures used to present the stimuli  
487 and the methods used to estimate the participants' performance (Heed & Azañon, 2014;  
488 Vanderclausen, Filbrich, De Volder, & Legrain, 2021). If the integrative hypothesis for  
489 interpreting slope changes during TOJ is correct, this would mean that our participants were  
490 less likely to integrate visual stimuli with nociceptive stimuli than they would with other  
491 types of stimuli. However, this conclusion is conditional on the fact that slopes have been  
492 correctly estimated, as this parameter may be more difficult to estimate than thresholds  
493 with a relatively small number of trials (Kingdom & Prins, 2010).

494 A significant difference between slope values was only observed when comparing the  
495 performance of the participants having received thermo-nociceptive stimuli selectively  
496 activating C fibers to those having received nociceptive stimuli above the threshold of  $A\delta$

497 fibers. This could possibly be accounted for by the fact that the sensation evoked by C-fiber  
498 stimuli is often considered as being poorly defined in terms of location and timing compared  
499 to the sensation elicited by A $\delta$ -fiber stimulations (Plaghki & Mouraux, 2005), making their  
500 temporal order judgments more difficult (Manfron, Filbrich et al., 2020).

501 In everyday life, the different sensory inputs arising from the same object generally  
502 stimulate their respective receptors at the same time and, although the generated inputs are  
503 transmitted to the brain with different latencies, we are still able to perceive them as  
504 simultaneous. The lag between each input is not perceived as long as they fall within the  
505 same time-window of integration, which tolerates a margin of error (e.g. Colonius &  
506 Diederich, 2004; Fujisaki et al., 2004; Morein-Zamir et al., 2003; Spence & Squire, 2003;  
507 Sugita & Suzuki, 2003). However, it is not possible to determine the extent of this time-  
508 window of interactions for a given situation since it varies according to many different  
509 factors, such as the sensory modality of the inputs, their implied link of causality, their  
510 spatial congruence, the attention allocated to them, the memory of past experiences as well  
511 as the respective intensity and duration of the stimuli (Colonius & Diederich, 2004; Fujisaki  
512 et al., 2012; Meredith et al., 1987; Stein & Meredith, 1993). There are two hypotheses that  
513 have been put forward to explain how such temporal binding of stimuli of different sensory  
514 modalities within that time-window is achieved. Whereas some authors proposed an  
515 overlapping of the discharge trains of multisensory neurons elicited by each sensory input,  
516 as suggested by electrophysiological recordings of single cells in the superior colliculus of the  
517 cat (Meredith et al., 1987), others rather suggested a resynchronization of the input of each  
518 sensory modality on the basis of the speed of their respective afferents (e.g. Colonius &  
519 Diederich, 2004). Considering somatosensory inputs, both the speed of the afferent fibers  
520 and the peripheral conduction distance could influence the ability of the brain to  
521 resynchronize different sensory inputs.

522 Finally, conversely to daily life situations in which multisensory interactions are shaped by  
523 past experiences and often concern different inputs that arise from the same sensory event  
524 (e.g. Macaluso et al., 2016; Welch, 1999), in experimental research the sensory modalities  
525 are often manipulated by basic and distinct stimuli. In that context, it might therefore be  
526 necessary to artificially introduce a temporal lag between the different stimuli for  
527 participants to perceive them simultaneously. It is also worth noting that multisensory



528 research often uses brief stimuli with sharp onsets, while in more ecological environmental  
529 situations, multisensory interactions are also supported by tonic and long-duration  
530 stimulations. The techniques used in present and previous studies regarding visuo-  
531 nociceptive interactions mostly targeted activation of the quickly-responding cutaneous  
532 thermo-nociceptors that preferentially respond to phasic stimulation. Slow-adapting thinly-  
533 myelinated and unmyelinated fibers were also described to respond preferentially to more  
534 tonic stimulation profiles (Bromm & Treede, 1984; Meyer & Campbell, 1981; Schepers &  
535 Ringkamp, 2010; Treede et al., 1998; Treede et al., 1995). It might be relevant to use other  
536 stimulation techniques and procedures that preferentially activate those receptors to  
537 investigate whether multisensory interactions with thermo-nociceptive stimuli applied  
538 distantly could be facilitated by the activity of nociceptors more sensitive to sustained  
539 stimulation.

540 In conclusion, the present study demonstrated that presenting visual and thermo-  
541 nociceptive stimuli at the same location decreases the necessary time lag between the two  
542 stimuli to perceive them as presented first equally often. This could suggest that spatial  
543 congruence between a visual and a nociceptive stimulus, by increasing their interactions,  
544 could facilitate the resynchronization of the brain of their respective times of arrival. The fact  
545 that spatial congruence shortens the time interval at which the two stimuli could be  
546 perceived as presented first equally often, with no evidence of affecting judgement  
547 precision, may suggest mutual attentional facilitation rather than integrative mechanisms,  
548 although the two putative mechanisms are not mutually exclusive. It is important to note  
549 that previous studies on visuo-nociceptive interactions only measured responses  
550 preferentially generated by A $\delta$  fiber activity. For the first time, we have shown indexes of  
551 interactions between visual stimuli and thermal stimuli specifically and selectively activating  
552 C fibers. As A $\delta$  and C fibers do not have the same physiological properties and give rise to  
553 qualitatively different sensations, it would be interesting for future experiments to test  
554 whether they are involved in the same way in multisensory interactions.

555

556 **Data Availability Statements**

557 The datasets generated during and/or analyzed during the current study are available from  
558 the corresponding author on reasonable request.

559

#### 560 **Declaration of competing interest**

561 None

562

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566

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