

The influence of visual experience and cognitive goals on the spatial representations of nociceptive stimuli

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Abstract

Localizing pain is crucial because it allows for detecting which part of the body is being hurt and identifying in its surrounding which stimulus is producing the damage. Nociceptive inputs should therefore be mapped according to somatotopic ("which limb is stimulated?") and spatiotopic representations ("where is the stimulated limb?"). Because the body posture constantly changes, the brain has to realign the different spatial representations, for instance when the arms are crossed with the left hand in the right space and vice versa, to adequately guide actions towards the threatening object. Such ability is thought to be dependent on past sensory experience and contextual factors. We compared performances of early blind and normally sighted participants during temporal order judgement tasks. Two nociceptive stimuli were applied, one on each hand, with the hands either uncrossed or crossed. Participants reported which stimulus they perceived as first presented, according to either its location on the body or the position of the stimulated hand, respectively, prioritizing anatomy or external space as task-relevant reference frame. Relative to the uncrossed posture, sighted participants' performances were decreased when the hands were crossed, whatever the instruction be. Early blind participants' performances were affected by crossing the hands during spatial instruction, but not during anatomical instruction. These results indicate that nociceptive stimuli are automatically coded according to both somatotopic and spatiotopic representations, but the integration of the different spatial reference frames depends on early visual experience and ongoing cognitive goals, illustrating the plasticity and the flexibility of the nociceptive system.

Keywords: Nociception, Early blindness, Cognitive goals, Spatial cognition, Crossmodal plasticity, Temporal order judgment

1. Introduction

One of the most relevant yet unresolved questions in pain research is how the brain localizes pain on the body.³⁸ Most research so far focused on the ability to localize nociceptive stimuli based on the somatotopic organization of the brain,^{1,9,10,12,32} anatomically mapping the body surface from the ordered projections of receptive fields.⁴² However, because the position of the body limbs in external space constantly changes, such a spatial representation might be inefficient to appropriately localize the harmful stimulus around the body.³⁸ The spatiotopic representation considers the relative position of the body part receiving the stimulus in external space.⁵² Using external space as reference frame, it allows the brain to identify the object in contact with the body, and spatially guide actions towards this object,¹³ such as defensive behaviors.^{29,38}

The spatiotopic representation was evidenced, both for touch and nociception, using temporal order judgment (TOJ) tasks,^{6,8,17,19–21,30,44–46,54} during which participants determined the order of appearance of 2 successive somatosensory stimuli, one applied on each hand. Temporal order judgment tasks are typically less accurate when their arms are crossed, as compared to an uncrossed posture, when reporting which hand is perceived as having been stimulated first. That effect is accounted for by the fact that the somatotopic representation mismatches the spatiotopic one (when crossed, a contact on the left hand is coming from the right part of space).⁵⁴ The sensitivity of TOJ to posture indicates that nociception and touch, in addition to the somatotopic coding, are automatically coded according to spatiotopic coordinates taking into account the location of the hands in external space.³⁰ In addition, crossing the hands decreases the perceived intensity of nociceptive stimuli,^{27,51} highlighting the crucial role of spatial representations in pain processing. Interestingly, this automatic and default spatiotopic coding of somatic stimuli is not innate but shaped by early visual experience.³⁰ Accordingly, tactile TOJ performance of congenitally blind individuals is not affected by crossing the hands,^{17,19,44} witnessing their preferential reliance on somatotopic representations to localize somatosensory inputs.¹⁸ However, recent data showed that tactile TOJ of congenitally blind individuals can be affected by body posture when spatiotopic coordinates are relevant according to the goal of the task.²⁰

Using TOJ tasks, we investigated the role of (1) past visual experience—by comparing performances of sighted and congenitally blind participants—and (2) ongoing cognitive goals—by

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manipulating spatial coordinates' priorities through task instructions—in shaping the spatial representations of nociceptive stimuli. Participants responded to the nociceptive stimuli according to either their anatomical location or the spatial location of the stimulated hand. It was hypothesized that body posture would decrease sighted participants' performances, whatever the response condition is, whereas blind participants' performance would only be affected under spatial instruction. Present data highlight the role of multisensory interactions in shaping nociceptive processing, and suggest that the spatial representations of nociceptive inputs are not fixed, but rather plastic and flexibly adjusted to contextual priorities.

2. Methods

2.1. Participants

Sixteen normally sighted participants took part in experiment 1. One participant was excluded because she could not properly achieve task requirements (see Analyses). The remaining 15 participants (12 women) had a mean age of 24 years ($SD = 2.6$). Twelve of these participants were right-handed, according to the Flinders Handedness Survey.⁴¹ Ten early blind participants (mean age = 38, $SD = 13$; 1 woman; 8 right-handed, 1 ambidextrous) took part in experiment 2. Ten normally sighted participants were recruited as controls and matched to blind participants according to age and sex (mean age = 37, $SD = 13$; 1 woman, 8 right-handed). None of the participants reported prior history of severe neurological, psychiatric, or chronic pain disorders, traumatic injury of the upper limbs in the past 6 months, cutaneous lesion of the hands' dorsa, regular use of psychotropic drugs, as well as intake of analgesic drugs (eg, NSAIDs and paracetamol) within the 12 hours preceding the

experiment. Normally sighted participants had normal or corrected-to-normal vision, meaning that some of them had mild visual deficits (eg, mild myopia) completely corrected by glasses or contact lenses. Early blind participants were recruited according to blindness attributed to peripheral deficits (**Table 1** for a complete description of blind participants). They were all considered as totally blind from birth. One of them (participant EB6) had very poor vision from birth and became definitively and totally blind consecutive to enucleation of the eyes at 18 months; he was therefore considered as early blind. Written informed consents were obtained from all participants, and all experimental procedures were approved by the biomedical local ethics committee (Comité d'Ethique hospitalo-facultaire, Saint-Luc University Hospital & Université catholique de Louvain, approval number: B403201214265) and conformed to the Declaration of Helsinki. All participants received financial compensation for their participation.

2.2. Stimuli and apparatus

Nociceptive stimulations consisted of radiant heat stimuli delivered onto the skin of the hands' dorsa by means of 2 infrared CO₂ laser stimulators (wavelength 10.6 μm) (Laser Stimulation Device; SIFEC, Ferrières, Belgium). The power of the output stimulation was regulated using a feedback control based on an online measurement of the skin temperature at the site of stimulation by means of a radiometer whose field of view was collinear with the laser beam.¹⁵ This allows defining specific skin temperature profiles. The laser beams were conducted through 10-m optical fibers. Each fiber ended with a head containing the optics used to collimate the laser beam to 6 mm diameter at the target site. Each laser head was held upon each participant's

Table 1
Description of the early blind participants.

Participant	Gender; Age	Handedness	Profession/Educational level	Visual perception	Onset of blindness	Cause of blindness	Braille	Cane	Musical instrument	Musical experience	Other
EB1	M; 29	R	College degree	None	Birth	Leber congenital amaurosis	Yes	Yes	No	/	Various sport activities
EB2	M; 23	R	Some college	None	Birth	Congenital cause*	Yes	Yes	No	/	/
EB3	M; 41	R	College degree	None	Birth	Leber congenital amaurosis	Yes	Yes	Piano/organ	>5 yrs	Torball
EB4	M; 41	R	Teacher/college degree	None	Birth	Anterior chamber cleavage syndrome (Peters syndrome)	Yes	Yes + Dog	Piano/drums/flute	>5 yrs	Hearing aids
EB5	M; 32	L	Some college	None	Birth	Hereditary retinal dysplasia	Yes	Yes	Guitar	>4 yrs	Slight auditory loss
EB6	M; 66	R	College degree	None	18 months	Bilateral retinoblastoma	Yes	Yes	Church organ	>9 yrs	/
EB7	F; 36	R	Phone sale until 2006/official high school	None	Birth	Severe corneal dysplasia	Few	Yes + Dog	Drums	Only few months	/
EB8	M; 33	R	Some college	None	Birth	Persistent hyperplastic primary vitreous involving both eyes	Yes	Yes	Musical keyboard	>10 yrs	/
EB9	M; 50	R	College degree	None	Birth	Leber congenital amaurosis	Yes	Yes	Piano	>3 yrs	/
EB10	M; 26	Ambi	Receptionist/official high school	None	Birth	Leber congenital amaurosis	Yes	Yes	Drums, piano, harmonica, guitar	>5 yrs	ADHD syndrome

Age in years.

* No additional details available.

ADHD, attention deficit and hyperactivity disorder; Ambi, ambidextrous; EB, early blind; F, female; L, left; M, male; R, right.

hand by means of articulated arms attached to a camera tripod system (Manfrotto, Cassola, Italy). Each laser head was fixed into a clamp attached to a 3-way head affording displacements of the target site of the laser beam perpendicularly oriented to the target's dorsum by means of several sliders going in all directions (**Fig. 1**). Laser beams were displaced after each stimulus. Stimuli duration was 100 ms. Stimuli were composed of a 10-ms heating ramp dedicated to reach the target temperature, followed by a 90-ms plateau during which the skin temperature was maintained at the target temperature. Heating was then stopped. The target temperature was determined for each participant's hand according to individual activation threshold of nociceptive thinly myelinated A δ fibers. Thresholds were estimated by means of an adaptive staircase procedure using reaction times (RTs) to discriminate detections triggered by A δ -fiber inputs (RT < 650 ms) from detections triggered by C-fiber inputs (RT \geq 650 ms).¹⁵ Participants were asked to press a button with the nonstimulated hand as soon as they felt something on the stimulated hand. Any RT equal or superior to 650 ms led to a temperature increase of 1°C for the next stimulus. On the contrary, any RT inferior to 650 ms led to a decrease in temperature of 1°C. The procedure started at 46°C and lasted until 4 reversals were encountered. The mean value of the 4 temperatures that led to a reversal was considered as the threshold. View of the hands was prevented during threshold estimation in sighted participants. Next, 5°C was respectively added to the threshold values of the left and right hands to determine the target temperatures of the experimental

stimuli. To avoid unbalanced intensity perception between the 2 hands, and, consequently, attentional shift and perceptual bias towards stimuli of one of the hands,²¹ stimuli temperatures were adapted so that stimuli were perceived as equally intense between the 2 hands. To these aims, pairs of laser stimuli were delivered, one on each hand, and participants were then asked to report whether the stimulations on the 2 hands were perceived as equally intense and whether the sensation elicited on the 2 hands was similar. If not, temperatures were slightly increased or decreased until similar perceived intensity between the left and the right hands was reached. Such adaptation was needed for 5 of the early blind and 7 of the normally sighted participants, and temperatures were adapted by maximum 2°C as compared to the initial target values (ie, threshold +5°C). Stimuli at such temperature values elicited a clear and vivid pricking sensation perceived as slightly painful. During the experiment, after each block of stimuli, participants were asked to describe the overall sensation of the stimuli using a list of word descriptors (*not perceived, light touch, tingling, pricking, warm, and burning*), and to rate their overall intensity using a numerical scale (from 0 [*no sensation*] to 10 [*strongest sensation imaginable*]). The list of words was visually presented to the sighted participants and read out loud to the blind participants. Sensation evaluation and intensity rating were only intended to ensure that stimuli were still perceived as pricking and equally intense between the 2 hands; they were not further analyzed. If necessary, stimuli temperatures were adapted for the upcoming block. Such adaptation was made for only 2 early blind and 5 normally sighted

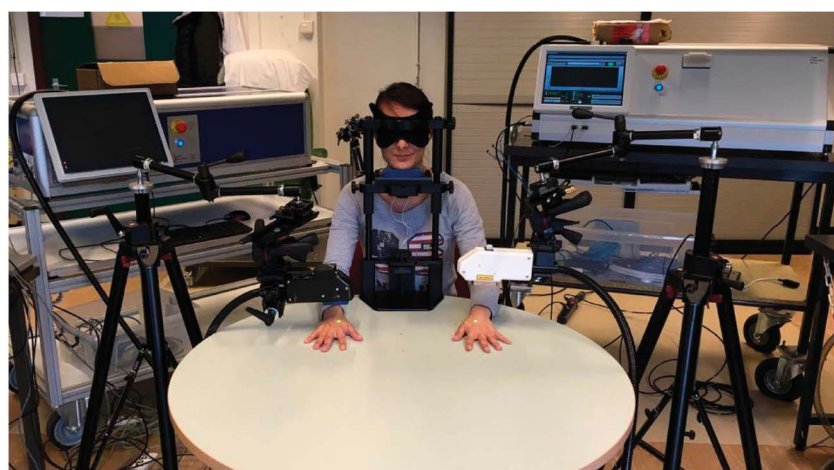


Figure 1. Experimental design of experiments 1 and 2. Two temperature-controlled CO₂ laser stimulators were used to activate A δ fibers. Laser beams were displaced after each trials on the hands' dorsa using camera tripod systems. Temporal order judgement tasks were performed with the hands in either an uncrossed (A) or a crossed (B) posture. Sighted participants performed the tasks blindfolded. Permission for publishing was obtained from the participant appearing in this picture.

participants using an increase of maximum 1°C as compared to the initial values.

2.3. Procedure

The same procedure was used for experiments 1 and 2. Participants were sitting on a chair, with their hands' palms laid down on a table in front of them. During the uncrossed hands posture condition (see below), the tips of the 2 index fingers were separated by a distance of ~30 cm. During the crossed hands posture condition, the same distance separated the tips of the 2 fourth fingers. Reference fingers were chosen to ensure similar distance between the hands during the 2 posture conditions. Distance between the reference fingers and the edge of the table was of ~40 cm (**Fig. 1**). Participants' head was placed in a chin-rest to minimize head movement during the experiment. Noises from experimental devices were covered by a white noise played through earphones that the participants wore during the whole experiment. The sighted participants were blindfolded with an eye mask.

Participants were presented with 4 blocks of 40 trials each. Each trial consisted in pairs of nociceptive stimuli, one applied on each hand, separated by 24 possible stimulus-onset asynchronies (SOA): ± 10 , ± 15 , ± 30 , ± 45 , ± 60 , ± 75 , ± 90 , ± 150 , ± 200 , ± 400 , ± 500 , and ± 600 ms. Negative values indicated that the left hand was stimulated first, whereas positive values indicated that the right hand was stimulated first. Within each experimental block, the presented SOA for a given trial was selected according to the participant's performance in all the previous trials, using the adaptive *psi* method.³⁴ Based on a Bayesian framework, this adaptive procedure estimates the posterior distribution of the parameters of interest by minimizing their expected entropy (ie, uncertainty) trial by trial, so that the SOA selected at each trial gives the most information to estimate the parameters of interest without probing extensively all the possible SOA (see Ref. 23 for further details about the use of the *psi* method in the frame of TOJ tasks). Two of the 4 blocks were performed with the hands in an uncrossed posture and the 2 other blocks in a crossed posture (ie, arms crossed over the body midline). Within each posture condition, participants performed one block in which they had to respond according to an anatomical instruction (*"Which hand was stimulated first?"*) and one block in which a spatial instruction was used (*"From which side of space came the first stimulus?"*). The order of the *posture* and *instruction* conditions was counterbalanced across participants. Participants had to verbally report either on which hand they felt the first stimulus or from which side of space came the first stimulus of the pair, by saying *"left"* or *"right"* out loud. Participants' responses were encoded by the experimenter on a keyboard triggering the next trial 2000 ms later. Time interval between 2 trials varied from 5 to 10 seconds. During that time interval, the 2 laser beams were displaced on the participant's hands to avoid skin overheating or habituation. The task was unspeeded, but the participants were instructed to be as accurate as possible. No feedback was available regarding their performance in the task.

A practice session preceded the experiment and consisted of 4 blocks of 5 trials each, one block per hand posture and per instruction condition (ie, uncrossed vs crossed, and *"which hand"* vs *"which side of space"*). Only 2 among the largest SOA were presented during this practice session (± 150 and ± 200 ms). One block lasted between 10 and 15 minutes. A 10-minute break was imposed to the participants between the experimental blocks. The whole experiment lasted 2 to 3 hours, including the threshold measurement, the training session, and the experiment per se.

2.4. Measures

Aδ-fiber activation thresholds and stimulation intensities (corresponding to the averaged intensity used for each hand across the experimental blocks, ie, approximately 5°C added to the Aδ-fiber activation thresholds) were measured in degrees Celsius (°C).

Regarding TOJ performances, the proportion of left stimuli perceived as being presented first was computed as a function of SOA for each experimental condition. To allow for comparisons between the different conditions, responses during the crossed hands posture with spatial instruction were coded according to the stimulated hands. For each participant, data were fitted online with the logistic function, ie, $f(x) = 1/(1 + \exp(-\beta(x - \alpha)))$,²³ used to derive the measures of interest: the threshold (α) and the slope (β) of the function, estimated trial by trial. The final estimates of the measures thus correspond to the last update of the parameter estimation.³⁵ In the present experiments, we were especially interested in the β parameter, which described the noisiness of the participants' responses, ie, the precision of their responses during the experiment.³⁴ In previous TOJ studies classically using the method of constant stimuli (ie, each of the SOA is presented a fixed number of times), the slope was used to derive the just noticeable difference, which denotes the minimal SOA value needed for the participants to correctly perceive the order of the 2 stimuli in a certain percentage of trials.^{22,30} The slope and other derived measures are classically used to index the impact of posture on TOJ performances both in sighted and blind participants: the steeper the fitted function, the better the participants' performance in the task.^{6,8,17,19–21,30,44–46,54} The α is the threshold of the function and corresponds to the SOA at which the participants reported the 2 stimuli as occurring first equally often (ie, the probability of 0.5). Accordingly, this measure corresponds to the point of subjective simultaneity (PSS) defining the amount of time (in milliseconds) with which one of the stimuli has to precede or follow the other one in order for the 2 stimuli to be perceived as occurring simultaneously.²² Although this parameter was not relevant for our research questions, it was taken into consideration to investigate the presence of potential biases towards the perception of the stimuli applied to one of the hands, which could have influenced the estimation of the slope. Indeed, in the frame of the adaptive *psi* method, the measures of the threshold and the slope are not completely independent and a large PSS value, indicating a bias in the perception of one of the 2 stimuli, could reduce the noisiness of the participant's responses because of the predictability of these responses. Because the *psi* method was based on a Bayesian approach, a prior probability distribution needed to be postulated, based on previous knowledge regarding the values of the parameter of interest.²³ For the present experiments, the prior distributions were set at 0 ± 20 and 0.06 ± 0.6 for the α and the β parameters, respectively.²³

Because we used an adaptive method, all the participants were not presented with the same sequence of SOA during the experiment, as it was adapted to each participant's performance. Therefore, a third nonstandard parameter was derived a posteriori from the present data: the mode of the presented SOA. This corresponded to the value of the SOA, among all the possible SOA, that was most frequently presented to a given participant during a particular condition of the experiment (in milliseconds). The mode of the presented SOA characterizes the probability distribution of the SOA values that were actually chosen for each participant and how this probability distribution was influenced by the experimental variables during the adaptation procedure of the method. Indeed, a significant difference between the modes of 2

experimental conditions would indicate that the SOA most frequently presented to the participant was larger in one condition relative to the other for the participant to be able to correctly determine the temporal order of the stimuli. In this case, a larger mode value would indicate that the task was more difficult to perform in this condition as compared to the other one. As such, the mode of the presented SOA was used as complementary index of participants' performance.

2.5. Analyses

Participants' data were excluded from statistical analyses if the threshold and slope of the psychometric function could not be reliably estimated during the 40 trials of one or several experimental conditions (ie, their respective estimates did not converge on a stable value on the past trials), indexing that their performance was too inconsistent and below chance level. Analyses were first performed on the A δ -fiber activation threshold and stimuli intensity values to ensure that no difference between hands or groups regarding these factors could have influenced the results. In experiment 1, comparison of activation thresholds and stimulation intensities was made using paired *t*-tests with *hand* as the factor (left vs right). In experiment 2, we used an analysis of variance (ANOVA) for repeated measures, adding the group as second factor (sighted vs blind).

Regarding TOJ values, one-sample *t*-tests were first performed to compare the PSS values to 0 for each condition of the *posture* and *instruction* factors, and each of the 3 groups, to examine the presence of potential biases. Next, the effects of the different factors on the PSS, slope, and mode of the SOAs values were compared by means of ANOVAs for repeated measures. For experiment 1, *posture* (uncrossed vs crossed) and *instruction* (anatomical vs spatial) were used as within-participants factors. For experiment 2, *group* (early blind vs normally sighted) was added as a between-participants factor. Greenhouse–Geisser corrections were used if necessary. Contrast analyses were conducted to detail significant interactions between 2 or more factors. Effect sizes were measured using partial eta squared for ANOVA and Cohen's *d* for *t*-tests. Significance level was set at $P \leq 0.050$.

3. Results

3.1. Experiment 1

3.1.1. Threshold and intensity values

Paired-sample *t*-tests revealed no difference between the A δ -fiber activation threshold values of the left hand ($M = 47.80^\circ\text{C}$, $SD = 1.52^\circ\text{C}$) vs the right hand ($M = 47.40^\circ\text{C}$, $SD = 1.77^\circ\text{C}$) in the sighted participants in experiment 1 ($t(14) = 0.72$, $P = 0.442$, $d = 0.26$). Similarly, no difference were found regarding the mean intensity of nociceptive stimuli between the left ($M = 52.55^\circ\text{C}$, $SD = 1.98^\circ\text{C}$) and the right ($M = 52.34^\circ\text{C}$, $SD = 1.98^\circ\text{C}$) hands ($t(14) = 0.39$, $P = 0.702$, $d = 0.26$).

3.1.2. Temporal order judgment values

Results of experiment 1 are illustrated in **Figure 2**. The *t*-tests showed that none of the PSS values from each posture and instruction conditions was significantly different from 0 (all $t(14) \leq 0.977$, $P \geq 0.345$, $d \leq 0.25$). The ANOVA performed on the PSS values revealed neither a significant main effect of the posture ($F(1,14) = 0.01$, $P = 0.941$, $\eta_p^2 < 0.01$), nor of the instruction

($F(1,14) = 0.56$, $P = 0.468$, $\eta_p^2 = 0.04$), nor significant interaction between the 2 factors ($F(1,14) < 0.01$, $P = 0.970$, $\eta_p^2 < 0.01$).

The analysis of the slope values showed a significant main effect of the posture ($F(1,14) = 37.34$, $P < 0.001$, $\eta_p^2 = 0.73$) with no significant effect of the instruction ($F(1,14) = 1.54$, $P = 0.235$, $\eta_p^2 = 0.10$) and no significant interaction between both factors ($F(1,14) = 0.33$, $P = 0.577$, $\eta_p^2 = 0.02$). This indicated that the slope values in the crossed posture ($M = 0.01$, $SD = 0.01$) was significantly lower than those in the uncrossed posture ($M = 0.03$, $SD = 0.01$), whatever the instruction be.

The analysis of the mode values did not reveal any significant effect of the posture ($F(1,14) = 2.01$, $P = 0.178$, $\eta_p^2 = 0.13$), of the instruction ($F(1,14) = 0.01$, $P = 0.921$, $\eta_p^2 < 0.01$), or any significant interaction between the 2 factors ($F(1,14) = 0.08$, $P = 0.781$, $\eta_p^2 < 0.01$).

3.2. Experiment 2

3.2.1. Threshold and intensity values

The ANOVA performed on the A δ -fiber activation thresholds did not show significant effect of the hand ($F(1,18) = 0.74$, $P = 0.400$, $\eta_p^2 = 0.04$), of the group ($F(1,18) = 0.33$, $P = 0.574$, $\eta_p^2 = 0.02$), or any significant interaction between the 2 factors ($F(1,18) = 0.24$, $P = 0.628$, $\eta_p^2 = 0.01$). Early blind participants thus had a similar A δ -fiber activation threshold ($M = 49.75^\circ\text{C}$, $SD = 3.91^\circ\text{C}$) than the sighted participants ($M = 50.55^\circ\text{C}$, $SD = 2.06^\circ\text{C}$). Similar results were obtained regarding the stimulation intensities because the analyses showed neither significant effect of the hand ($F(1,18) = 2.04$, $P = 0.171$, $\eta_p^2 = 0.10$), nor significant effect of the group ($F(1,18) = 0.85$, $P = 0.369$, $\eta_p^2 = 0.01$), or significant interaction between the 2 factors ($F(1,18) = 0.17$, $P = 0.688$, $\eta_p^2 = 0.01$). The averaged stimulation intensity used for the early blind group ($M = 54.77^\circ\text{C}$, $SD = 2.77^\circ\text{C}$) was comparable to that for the sighted group ($M = 55.73^\circ\text{C}$, $SD = 1.79^\circ\text{C}$).

3.2.2. Temporal order judgment values

Results of experiment 2 are illustrated in **Figures 3 and 4**. None of the PSS values were significantly different from 0 in the early blind group (all $t(9) \leq -0.54$, all $P \geq 0.224$, $d \leq 0.17$). In the sighted group, most of the PSS values were not significantly different from 0 (all $t \leq -1.91$, $P \geq 0.088$, $d \leq 0.60$), except for the PSS value in the uncrossed posture with anatomical instruction ($t(9) = -7.02$, $P < 0.001$, $d = 2.22$). With an averaged value of -10.12 ms ($SD = 4.56$ ms), this indicated that their judgments were slightly biased towards the right hand in this condition. The ANOVA did not reveal significant main effect neither of the posture ($F(1,18) = 2.22$, $P = 0.154$, $\eta_p^2 = 0.11$) nor of the instruction ($F(1,18) = 1.96$, $P = 0.179$, $\eta_p^2 = 0.10$). By contrast, this analysis showed a significant effect of the group ($F(1,18) = 6.25$, $P = 0.022$, $\eta_p^2 = 0.26$), indicating that the PSS values of normally sighted participant were more negative ($M = -5.60$ ms, $SD = 7.60$ ms) than those of the early blind participants ($M = 1.68$ ms, $SD = 10.32$ ms). In addition, a significant interaction between the *posture* and the *instruction* factors was observed ($F(1,18) = 5.60$, $P = 0.029$, $\eta_p^2 = 0.24$). Contrast analyses showed that during the uncrossed posture, the PSS value in the anatomical instruction condition ($M = -6.05$ ms, $SD = 9.57$ ms) was larger than that of the spatial instruction condition ($M = -0.80$ ms, $SD = 10.70$ ms; $t(19) = -2.15$, $P = 0.045$, $d = 0.48$). Such difference was not significant during the crossed posture ($t(19) = 0.54$, $P = 0.593$, $d = 0.12$). None of the other possible interactions was significant (all $F(1,18) \leq 0.22$, all $P \geq 0.643$, $\eta_p^2 \leq 0.01$).

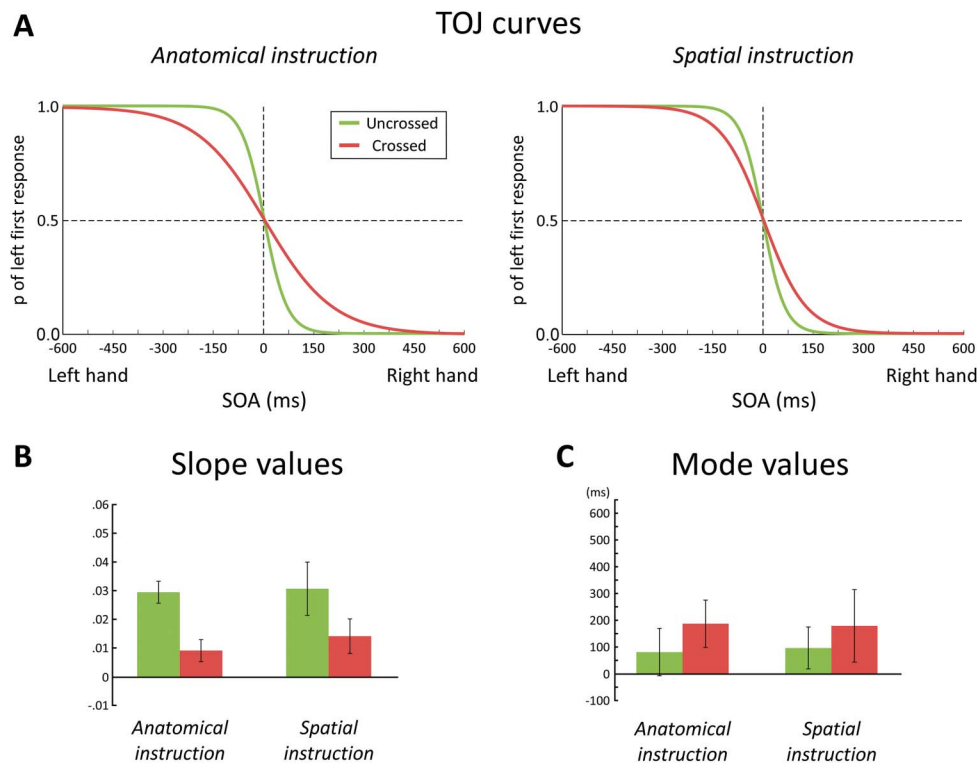


Figure 2. Nociceptive TOJ tasks of experiment 1. (A) Fitted curves of the psychometric functions from the data of 15 normally sighted participants according to the posture (ie, uncrossed vs crossed) and according to the instruction (ie, anatomical vs spatial) conditions. The x-axis represents the different possible SOAs. A negative value indicates that the left hand was stimulated first and a positive value indicates that the right hand was stimulated first. The y-axis refers to the proportion of trials in which the nociceptive stimulus applied on the left hand was perceived as being presented first. The lines represent the fitted curves computed by the adaptive logarithm for the uncrossed (green) and crossed (red) conditions. (B) Averaged slope values for each posture and instruction condition. The mean of the slope values was significantly lower in the crossed as compared to the uncrossed condition, whatever the instruction condition is. (C) Averaged mode values of the presented SOA according to each posture and instruction condition. Error bars represent confidence intervals calculated according to Cousineau's method for within-subject designs.¹⁶ SOA, stimulus-onset asynchronies; TOJ, temporal order judgment.

Regarding the slope values, the ANOVA showed a significant main effect of the group ($F(1,18) = 4.80$, $P = 0.042$, $\eta_p^2 = 0.21$), a significant main effect of the posture ($F(1,18) = 27.15$, $P < 0.001$, $\eta_p^2 = 0.60$), a significant main effect of the instruction ($F(1,18) = 4.68$, $P = 0.044$, $\eta_p^2 = 0.21$), and a significant interaction between posture and instruction ($F(1,18) = 7.23$, $P = 0.015$, $\eta_p^2 = 0.29$). We also observed a significant triple interaction between all factors ($F(1,18) = 6.47$, $P = 0.020$, $\eta_p^2 = 0.26$). None of the other interactions was significant (all $F(1,18) \leq 0.21$, all $P \geq 0.653$, $\eta_p^2 \leq 0.01$). Next, analyses were run separately in each group of participants with posture and instruction as within factors. For the early blind participants, we observed a significant main effect of the posture ($F(1,9) = 6.45$, $P = 0.032$, $\eta_p^2 = 0.42$), a significant interaction between the posture and instruction factors ($F(1,9) = 8.27$, $P = 0.018$, $\eta_p^2 = 0.48$), but no significant effect of the instruction ($F(1,9) = 2.26$, $P = 0.167$, $\eta_p^2 = 0.20$). Contrast analyses revealed no significant difference between the 2 postures in the anatomical instruction condition ($t(9) = -1.00$, $P = 0.343$, $d = 0.22$; $M \pm SD$ uncrossed = 0.03 ± 0.01 , $M \pm SD$ crossed = 0.03 ± 0.02). On the contrary, such difference was significant in the spatial instruction condition ($t(9) = 3.08$, $P = 0.013$, $d = 0.68$). Slope values were indeed smaller in the crossed posture ($M = 0.01$, $SD = 0.01$) than in the uncrossed posture conditions ($M = 0.04$, $SD = 0.03$) in the early blind group. By contrast, in the normally sighted group, only a significant main effect of the posture was observed ($F(1,9) = 64.82$, $P < 0.001$, $\eta_p^2 = 0.88$) with neither significant effect of the instruction ($F(1,9) = 2.44$, $P = 0.150$, $\eta_p^2 = 0.21$) nor significant interaction between the 2 factors ($F(1,9) = 0.03$,

$P = 0.87$, $\eta_p^2 < 0.01$). For the normally sighted participants, the slope values in the crossed posture condition ($M = 0.01$, $SD = 0.00$) were significantly lower than those in the uncrossed posture condition ($M = 0.02$, $SD = 0.01$). To summarize, results showed that the posture affected performances of the normally sighted participants, whatever the instruction condition is, whereas early blind participants' performance was only affected by the crossed posture when a spatial response was required.

Finally, the ANOVA performed on the mode of the presented SOA values showed a significant main effect of the posture ($F(1,18) = 34.3$, $P < 0.001$, $\eta_p^2 = 0.66$), a significant main effect of the group ($F(1,18) = 14.26$, $P = 0.001$, $\eta_p^2 = 0.44$), and a significant interaction between these 2 factors ($F(1,18) = 10.95$, $P = 0.004$, $\eta_p^2 = 0.38$). None of the other comparisons was significant (all $F(1,18) \leq 1.46$, all $P \geq 0.243$, all $\eta_p^2 \leq 0.08$). Analyses were then run separately in each group. In the early blind group, the ANOVA showed neither significant effect of the posture ($F(1,9) = 3.13$, $P = 0.11$, $\eta_p^2 = 0.26$) nor of the instruction ($F(1,9) = 3.19$, $P = 0.11$, $\eta_p^2 = 0.26$). The interaction between these 2 factors was just a bit above significance level ($F(1,9) = 4.01$, $P = 0.070$, $\eta_p^2 = 0.31$). In the sighted group, a significant effect of the posture was observed ($F(1,9) = 43.67$, $P < 0.001$, $\eta_p^2 = 0.83$), with the mode value in crossed posture being higher ($M = 420.50$ ms, $SD = 137.24$ ms) than that in the uncrossed posture condition ($M = 136.25$ ms, $SD = 122.24$ ms). The effect of the instruction did not reach significance ($F(1,9) = 0.01$, $P = 0.920$, $\eta_p^2 < 0.01$), neither did the interaction between the 2 factors ($F(1,9) = 0.02$, $P = 0.900$, $\eta_p^2 < 0.01$).

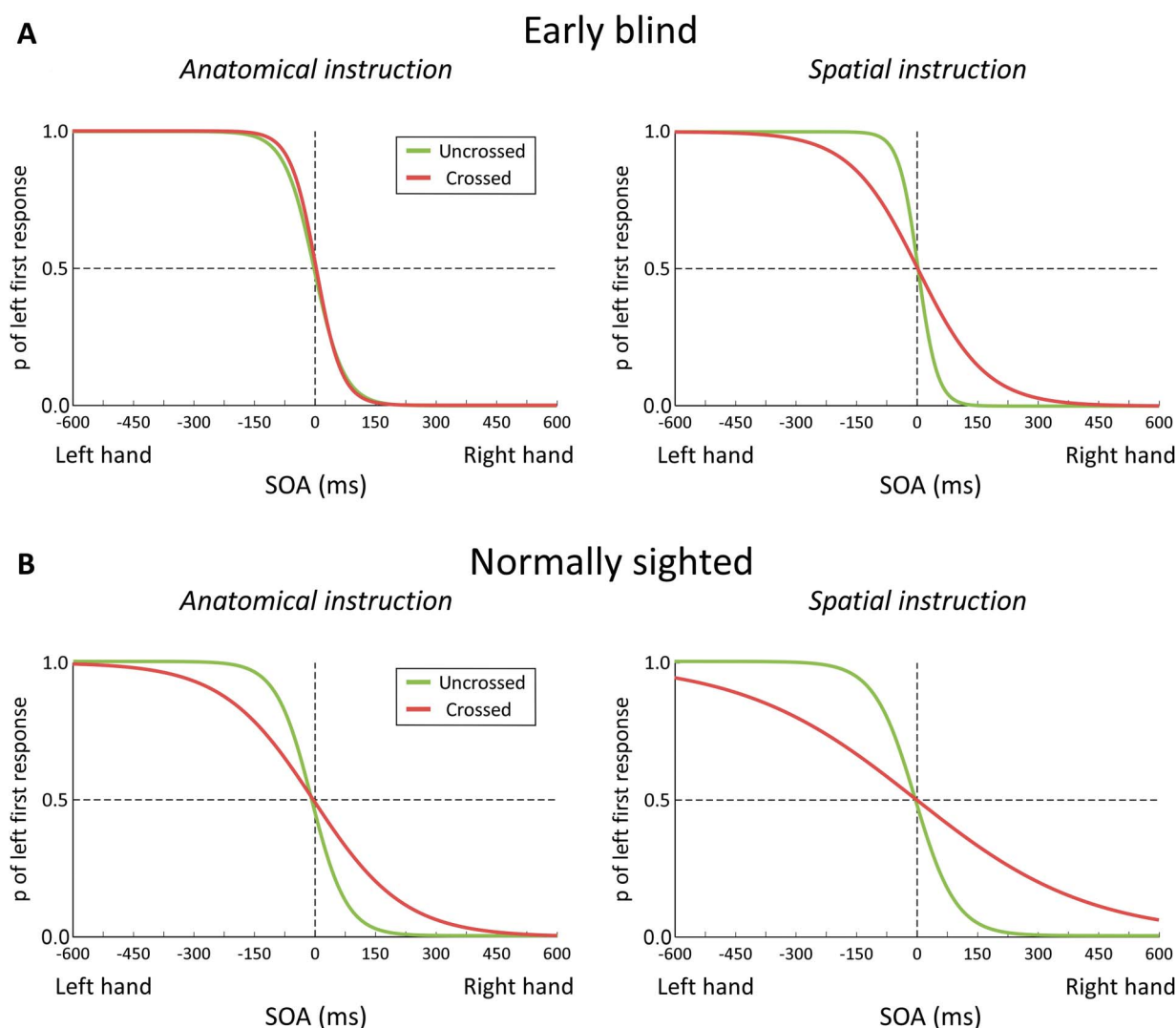


Figure 3. Nociceptive TOJ tasks of experiment 2. The figure illustrates the fitted curves of the psychometric functions from data of 10 early blind (A) and 10 sighted participants (B) according to the posture (uncrossed in green vs crossed in red) and the instruction conditions (anatomical on the left vs spatial on the right side of the figure). The x-axis represents the different possible SOAs. A negative value indicates that the left hand was stimulated first and a positive value indicates that the right hand was stimulated first. The y-axis refers to the proportion of trials in which the nociceptive stimulus applied on the left hand was perceived as being presented first. SOA, stimulus-onset asynchronies; TOJ, temporal order judgment.

4. Discussion

The objectives of the present experiments were to investigate the role of visual experience and cognitive goals in shaping the spatial representations of nociceptive stimuli. To this aim, we compared performances of normally sighted and early blind participants during TOJs of nociceptive stimuli, during which instructions favoured to use either an anatomical or a spatial representation. Importantly, TOJ tasks were performed with the hands either uncrossed or crossed over body midline, the latter condition being intended to generate a mismatch between somatotopic and spatiotopic representations. Results showed that sighted participants' performances were decreased in the crossed hands posture independently of which reference frame was task-relevant. On the contrary, performances of early blind participants were only affected by crossing the hands when they were requested to use a spatial response, whereas their performance was insensitive to the posture under anatomical instruction.

Influence of crossing the hands during cognitive tasks has been recurrently described in normally sighted people for both tactile and nociceptive stimuli.^{6,8,17,19–21,30,44–46,54} Such an

effect was interpreted as reflecting the ability of the brain to code the spatial location of somatosensory inputs according to spatiotopic reference frames.³⁰ Spatiotopic mapping has also been suggested to represent an important process, affording a common spatial framework for inputs from somatic and extrasomatic sensory modalities to be integrated in a peripersonal representation of the body.^{21,25} In this line, nociceptive and visual stimuli would optimize detection and reaction against physical threats around the body.³⁸ Together, this would suggest a default and major role of spatiotopic representations over somatotopic ones in the perception of somatosensory stimuli. However, the present data offer a new insight on this assumed dominance.

In normally sighted participants, results confirmed that nociceptive stimuli were mapped into spatiotopic representations taking body posture into account, in addition to be coded according to somatotopic representations.^{21,45} Because TOJ performance was similarly impaired under the 2 different task instructions, this indicated that both somatotopic and spatiotopic representations might be coactivated by default during spatial localization processing of nociceptive inputs. Hence, adapting

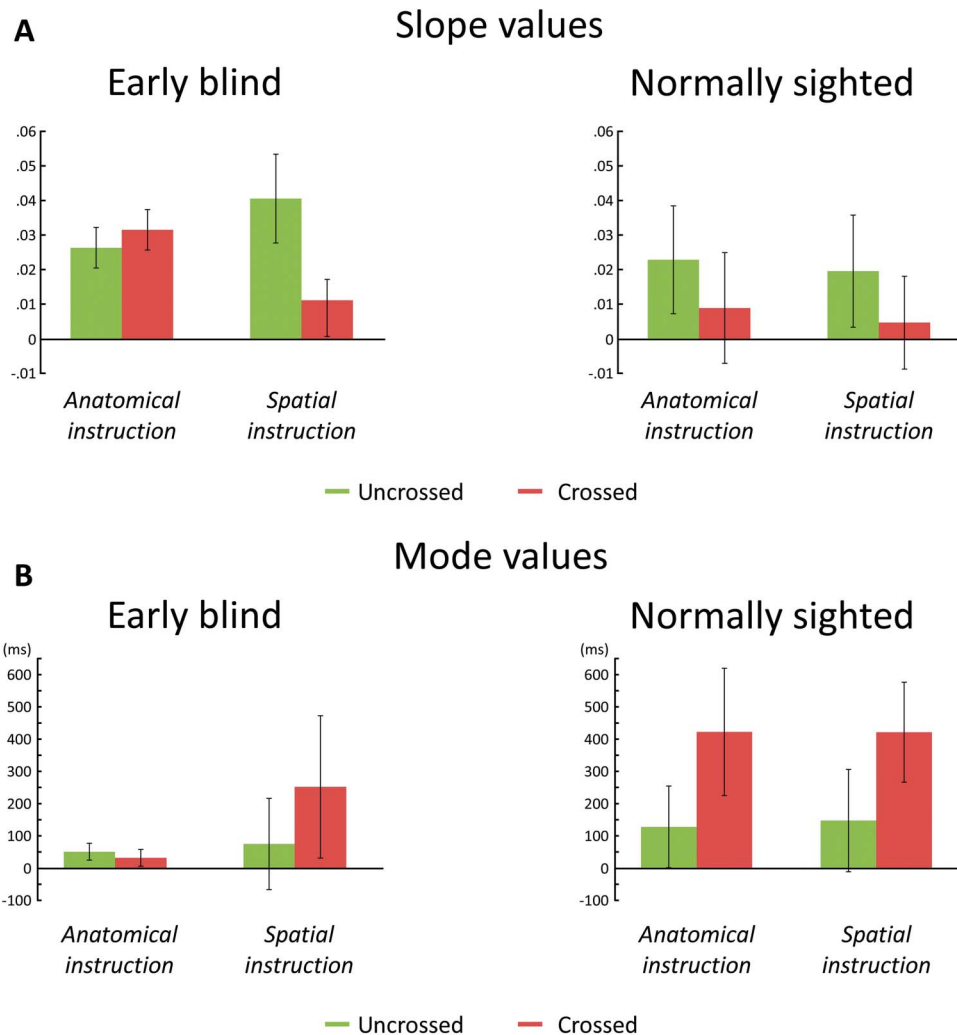


Figure 4. Slope and mode values of the nociceptive TOJ tasks of experiment 2. (A) Mean slope values for each posture (uncrossed in green vs crossed in red) and instruction conditions (anatomical on the left vs spatial on the right part of the graphs) for respectively the early blind (left) and normally sighted participants (right). In the early blind group, a lower averaged slope value was found in the crossed as compared to the uncrossed posture condition in the spatial instruction condition, whereas the performance of this group did not significantly differ according to the posture in the anatomical instruction condition. Conversely, in the sighted group, the averaged slope value was significantly lower in the crossed as compared to the uncrossed posture condition, whatever the instruction condition is. (B) Mean values of the mode of the presented SOA for each posture (uncrossed in green vs crossed in red) and instruction conditions (anatomical on the left vs spatial on the right part of the graphs) for respectively the early blind (left) and normally sighted participants (right). Although no significant difference between the conditions was evidenced in the blind group, significantly higher mode values were found in the sighted group in the crossed as compared to the uncrossed posture condition, irrespective of the instructions. Error bars represent confidence intervals calculated according to Cousineau's method for within-subject designs. ¹⁶ SOA, stimulus-onset asynchronies; TOJ, temporal order judgment.

cognitive goals by changing task instruction to stress external space-based coordinates was not enough to give advantage to the spatiotopic frame of reference and attenuate the crossing hands deficit in our experiments (see Ref. 20 for similar results with tactile stimuli). On the contrary, studies on tactile processing suggested that spatial coding of somatosensory stimuli was actually weighted depending on task demands and cognitive goals.^{5,6,8,26} Specifically, the results of these experiments indicated that the weight accorded to the spatiotopic representation could be attenuated under some conditions, but externally defined coordinates still had a robust influence on the participants' responses during tactile processing. Accordingly, the present data suggest that nociceptive stimuli are automatically coded according to both somatotopic and spatiotopic reference frames, but the weight respectively given to each reference frames during the localization processing of nociception would be more dependent on contextual factors such as cognitive goals.^{6,7}

In addition, results in early blind participants indicated that the assumed weighted activation of the spatiotopic reference frame of nociceptive stimuli might be driven by early visual experience. Indeed, a default advantage of somatotopic representations in congenitally blind people during touch localization had been recurrently suggested by means of behavioural as well as electrophysiological and neuroimaging data.^{18,19,43} However, regarding nociception and pain, being able to consider the position of the limbs in external space is of primary importance to protect the body from potential physical threats. Then, any individual should be able to take such spatial information into account, if not automatically, at least when it is relevant for the ongoing situation. Accordingly, we observed that a crossing hands deficit emerged in early blind participants in the spatial instruction condition, confirming that early blind participants were able to activate and use spatiotopic representations. Indeed, this finding suggests that the spatial representations at play when

localizing nociceptive events could be adapted according to the task requirements. We showed that making external space relevant by changing the instruction was sufficient to highlight the use of the spatiotopic reference frame in this group during TOJ tasks. These data are in line with a very recent study having shown the exact same pattern of results using a tactile TOJ task in early blind and normally sighted participants.²⁰ Other studies showed that in tactile motor coordination tasks, spatial external coordinates were actually used by congenitally blinds when task demands prioritized the external space.^{17,31} Taken together, these studies suggest a differential balance between the activation by default of the somatotopic and spatiotopic frames of reference in normally sighted and early blind participants during somatosensory perception.^{17,19,20} Following this idea, early blind individuals might have better abilities to inhibit the spatial responses when it is irrelevant for the ongoing activity, while formatting responses according to external space would be resistant to inhibition in sighted people, even when irrelevant to current behavioural goals.

The present studies therefore suggest that early visual experience shapes the way spatiotopic mapping of nociceptive stimuli develops, resulting in qualitatively different ways of processing nociception and pain in adulthood between early blinds and normally sighted individuals. Perhaps, as a result, some quantitative differences were observed between congenitally blind and normally sighted individuals regarding the perception of pain. For instance, Slimani et al.^{47,48} observed lower thresholds for heat and cold pain, as well as faster RTs to stimulations mediated by C-, but not Aδ-, fibers in congenitally blinds as compared to sighted controls. These authors have linked this “*hypersensitivity*” to pain in this population to higher levels of anxiety and enhanced attention to painful stimuli.³³ Altogether, the present and previous experiments on early blindness highlight that the plasticity of the nociceptive system depends on early sensory experience from any sensory modalities, including nonsomatic ones.

Our studies suggest that mechanisms underlying spatial representations of nociceptive inputs are similar to those evidenced for touch.³⁰ However, although the cortical substrates underlying the spatial representation of touch were extensively studied,^{3,4,11,14,19,28,39,49,50,53} they are still poorly understood for nociception.^{38,51} Premotor and posterior parietal brain areas have been largely shown to be involved in the spatial coding of tactile stimuli^{4,11,19,39,50,53} and in visuotactile crossmodal interactions.^{3,14,28,39,40} Nociceptive and painful stimuli were also shown to elicit brain activity in premotor and posterior parietal areas (see review in Ref. 2). However, it was suggested that the cortical regions classically observed in response to nociceptive and painful stimuli, such as cingulate and operculoinular cortices, were usually associated with a broader brain network involved in the detection of any sensory stimulus that might have an impact on the body's integrity.³⁷ Therefore, future studies should investigate the involvement of premotor and posterior parietal areas in mapping nociceptive inputs according to external spatial coordinates and in preparing spatially guided actions to protect the body's integrity.

The present data also offer a new insight on the so-called “*crossing hands analgesia*” according to which crossing the hands over the body midline decreases cortical responses to nociceptive stimuli and the perception of their intensity.^{27,51} Gallace et al.²⁷ interpreted this effect as reflecting a disruption of nociceptive processing in the brain. Accordingly, during unusual body posture such as when the arms are crossed, privileged connections with the nociceptive system would not be engaged,

especially those involved in spatial perception, resulting in a decrease of the cortical responses, which would in turn impede the processing of the intensity and its perception. However, based on present results, we propose an alternative hypothesis according to which, when the different reference frames are conflicting, the less accurate TOJ performance would reflect the effort that the brain has to make to prioritize the relevant reference frame and inhibit the irrelevant spatial code. We therefore hypothesize that the so-called analgesic effect observed during the crossed hands posture results from a lack of processing resources left out by the competition between the different spatial representations. In other words, resolving the conflict between the different reference frames and selecting the relevant spatial response requests attentional resources⁶ that are less available to process other stimulus features such as its intensity. Manipulating the attentional load was indeed shown to modulate nociceptive processing.³⁶

In conclusion, the present studies emphasize that localization of nociceptive stimuli is based on multiple mapping systems taking into account both the space of the body and external space. We showed that activating the different spatial reference frames is automatic but disentangling between the different spatial responses where there is a mismatch requires effort and depends on developmental and contextual weighting. Further experiments will be needed to disclose the cortical mechanisms underlying the spatial representations of pain and their impairments during pathological pain.²⁴

Conflict of interest statement

The authors have no conflicts of interest to declare.

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