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The temporal order judgement of tactile and nociceptive stimuli is impaired by crossing the hands over the body midline

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ABSTRACT

Crossing the hands over the midline impairs the ability to correctly judge the order of a pair of tactile stimuli, delivered in rapid succession, one to each hand. This impairment, termed crossed-hands deficit, has been attributed to a mismatch between the somatotopic and body-centred frames of reference, onto which somatosensory stimuli are automatically mapped. Whether or not such crossed-hands deficit occurs also when delivering nociceptive stimuli has not been previously investigated. In this study, participants performed a temporal order judgement (TOJ) task in which pairs of either nociceptive or tactile stimuli were delivered, one to each hand, while their arms were either crossed over the body midline or uncrossed. We observed that crossing the hands over the midline significantly decreases the ability to determine the stimulus order when a pair of nociceptive stimuli is delivered to the hands, and that this crossed-hands deficit has a temporal profile similar to that observed for tactile stimuli. These findings suggest that similar mechanisms for integrating somatotopic and body-centred frames of reference underlie the ability to localise both nociceptive and tactile stimuli in space.

1. Introduction

When a stimulus is delivered to the hand, the ability to determine its location in space relies on the integration of the information about where the stimulus is on the skin (on the basis of the somatotopic frame of reference) and where the hand is located in space (on the basis of the body-centred frame of reference, ie, relative to the body midline). One way to investigate the respective contribution of different frames of reference in the conscious localisation of somatosensory stimuli in space is performing a temporal order judgement (TOJ) task while the hands are crossed over the body midline.

In this task, 2 consecutive tactile somatosensory stimuli are delivered in rapid succession, one to either hand, and participants are required to indicate in which order the 2 hands were stimulated [3,11,24–28]. When the hands are crossed over the midline, the shortest temporal interval at which judgements are correct 75% of the time (between ~40 and ~70 ms when the hands are not crossed) doubles or triples [24,26,28]. This finding might seem surprising because determining the temporal order of stimulation of the 2 hands should rely on the location of the stimulus on the body, regardless of where the hands are located in space. However, the decrease in performance observed when the hands are crossed (the crossed-hands deficit) suggests the presence of a conflict between 2 competing frames of reference, 1 somatotopic and 1 body-centred, onto which somatosensory stimuli are automatically mapped [2,4,28]. Indeed, as the right hand usually occupies the right side of space (and vice versa for the left hand), when the hands assume an uncommon posture (eg, are crossed over the midline) an additional time is needed to take into account the conflicting information from the 2 frames of reference. The observation that the crossed-hands deficit is absent in congenital, but not late, blind people suggests that early vision is critical to develop an external frame of reference for tactile localisation [25].

By recording the subjective pain ratings and the electrophysiological responses elicited by both nociceptive and nonnociceptive

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somatosensory stimuli, we recently demonstrated that the integration of information between somatotopic and body-centred frames of reference is impaired when the hands are crossed over the midline, for both pain and touch [5], an effect possibly mediated by frontoparietal multimodal cortical areas [1,13]. Therefore, we hypothesized a possible effect of crossing the hands on the temporal perception of nociceptive stimuli. Such effect has never been investigated using nociceptive somatosensory stimuli, probably because of the difficulty in delivering, in rapid succession, pairs of nociceptive stimuli that are both selective (ie, that do not coactivate Aβ fibres), and sufficiently transient. We recently characterised the nociceptive selectivity of low-intensity intraepidermal stimulation (IES) [20], which overcomes this problem. Here, we used pairs of IES to test whether a crossed-hands deficit is observed using nociceptive stimuli.

2. Methods

2.1. Participants

Fifteen healthy volunteers (7 women) aged between 22 and 33 years (mean ± SD 26.4 ± 3.9 years) participated in this study, after giving written informed consent. Handedness was assessed in each participant with the Edinburgh Inventory [22]. Eleven participants were right-handed and 4 were ambidextrous. Three participants were excluded from analyses as a result of the low goodness-of-fit of their data; thus, 12 participants (4 women and 8 men; mean age 26.5 ± 4.3; 9 right-handed and 3 ambidextrous) remained in the sample. We did not recruit professional musicians because they have been demonstrated to perform differently from the rest of the population in TOJ tasks [11]. All procedures were approved by the local ethics committee.

2.2. Design

We used a 2×2 repeated-measures design with Modality (2 levels: nociceptive and tactile) and Position (2 levels: uncrossed and crossed) as experimental factors. Nociceptive and tactile stimuli were delivered in separate and alternating blocks. A pair of stimuli, one delivered to either hand, was presented in each trial. For each modality, participants had their hands uncrossed in half of the blocks and crossed over the midline in the other half of the blocks.

2.3. Stimuli

Nociceptive stimuli consisted of IES (3 pulses, each lasting 500 μs, with an interpulse interval of 5 ms) (Digitimer DS7, Digitimer UK) delivered with a stainless steel concentric bipolar needle electrode, consisting of a needle cathode (length, 0.1 mm; Ø, 0.2 mm) surrounded by a cylindrical anode (Ø, 1.4 mm) [8]. When low-intensities are used (eg, twice the perceptual threshold) IES activates selectively Aδ nociceptive afferents, without coactivating Aβ tactile mechanoreceptors [20]. Tactile stimuli consisted of vibrations (290 Hz; 10 ms duration) produced by a TE-22 signal generator (vibrating surface 1.6 cm × 2.4). The IES electrodes and the vibrotactile stimulators were attached on the dorsum of the fourth digit of both hands, on the proximal and distal phalange, respectively. The intensity of both nociceptive and tactile stimuli was twice the participant's perceptual threshold. Perceptual thresholds were estimated by using an adaptive staircase procedure [20]. After the first staircase reversal (ie, when the stimulus was detected if previously undetected, or when the stimulus was undetected if previously detected), the step size was reduced. The procedure was terminated after the occurrence of 4 staircase reversals at the final step size. Thresholds were estimated by averaging the intensity of the stimuli at which these reversals occurred. At a stimulus intensity corresponding to twice the perceptual threshold, IES selectively activates Aδ nociceptive fibres. None of the participants reported painful sensations upon stimulation. This is in agreement with previous reports that the sensation evoked by IES delivered at twice the perceptual threshold is purely noxious with minimal discomfort such as the feeling of a light touch and sometimes non-painful pricking [7].

2.4. Procedure

Participants sat comfortably, resting their arms on a table placed in front of them, in a dimly lit, temperature-controlled room. During the experiment, participants kept their eyes closed and wore headphones that delivered white noise, to mask any sound from the stimulators. There were 16 blocks in total. In 8 blocks nociceptive stimuli were delivered, and in the other 8 tactile stimuli were delivered. For each modality, 4 blocks were performed while the participants had their hands uncrossed and 4 while they crossed their hands over the midline. The order of uncrossed and crossed blocks was pseudorandomized, with no more than 2 consecutive blocks using the same position, and counterbalanced across participants. In half of the crossed blocks participants had their left arm over their right arm, and in the other half they had their right arm over their left arm. The distance between the fourth digit of the right and left hands (ie, the digits where the stimulators were attached) was approximately 40 cm in both the uncrossed and crossed positions. Each block consisted of 48 trials. Pairs of stimuli were delivered at 16 stimulus onset asynchronies (SOAs; −600, −400, −250, −100, −70, −50, −30, −15, +600,+400,+250,+100,+70,+50,+30,+15 ms; negative figures indicate that the first stimulus was delivered to the left hand). In half of the trials the first stimulus was delivered to the left hand, and in the other half the first stimulus was delivered to the right hand. Participants reported which hand received either the first stimulus ('respond-to-first', in half of the blocks) or the second stimulus ('respond-to-second'), by pressing a button positioned under the index finger of each hand. Importantly, it has been demonstrated that the crossed-hands deficit in the TOJ of tactile stimuli is not due to a response conflict between the anatomical code of the responding hand (eg, left) and the side of space where that hand is placed (eg, right) [24,26]. Participants were instructed before each block on whether they had to respond to the first or the second delivered stimulus. Half of the participants used the 'respond-to-first' mode in the first 8 blocks and the 'respond-to-second' mode in the remaining 8 blocks, and the other half of the participants did the reverse. Participants were instructed to respond as accurately and as rapidly as possible. If a response was not given within 3000 ms from the onset of the second stimulus, the trial was considered invalid and that interval was automatically repeated at the end of the block until a valid response was given. Four practice blocks, one for each combination of modality and position, of 16 pairs of stimuli each were administered before the beginning of the experiment.

2.5. Just noticeable difference and point of subjective simultaneity analysis

The order judgement probabilities in all conditions (nociceptive uncrossed, nociceptive crossed, tactile uncrossed, and tactile crossed) were fitted with a cumulative density function of a Gaussian distribution (Gaussian cumulative function, GCF; Appendix A). Individual subject data with a goodness-of-fit coefficient (R^2) lower than 0.6 in at least 1 of the 4 experimental conditions, were not included in group analyses. This led to the exclusion of 3 participants. The curves fitted with the GCF were used to determine the just noticeable difference (JND) and the point of subjective simultaneity (PSS) values, in each subject, for each of the 4 conditions. In TOJ tasks, the JND is defined as the SOA at which the response of the subject is correct in 75% of the trials, and the PSS is defined as the SOA at which the response of the subject is correct in 50% of the trials (ie, the SOA at which the 2 stimuli are perceived as simultaneous). JND and PSS values were obtained for both pooled and individual data. Statistical analyses were performed on the individual data by a 2-way, repeated-measures analysis of variance (ANOVA) with Modality (nociceptive and tactile) and Position (uncrossed and crossed) as experimental factors.

2.6. The Gaussian flip model

Because previous TOJ studies that used tactile stimuli have demonstrated that the Gaussian flip function (GFlipF) may be a better fit for the data in the crossed condition [28], the order judgement probabilities in the nociceptive crossed and tactile crossed conditions were also fitted with a GFlipF equation. To test whether the GFlipF represented a better fit for crossed data in both nociception and touch, the goodness-of-fit coefficients (R^2) of the GCF and GFlipF fitting equations were compared for the crossed blocks in the 2 modalities by a 2-way, repeated-measures ANOVA with Fitting (2 levels, GCF and GFlipF) and Modality (2 levels, nociceptive and tactile) as experimental factors.

The Gaussian flip model assumes that the order judgement probability in the crossed condition is reversed, compared to that in the uncrossed condition, by a flip probability that decays with time (ie, SOA) in a Gaussian manner. The standard deviation (σ_f) of this Gaussian curve corresponds to the width of the time window where there is a higher probability of judgement reversal. To test whether the width of this time window was similar in nociception and touch, the σ_f values were compared between the nociceptive crossed and tactile crossed blocks by a paired *t* test.

Finally, to test whether there was any side bias in the probability of order judgement reversals, the height of the Gaussian curve (which reflects the probability of inversion from left-first to right-first; A_l, Fig. 3), and the depth of this curve (which reflects the probability of inversion from right-first to left-first; A_r, Fig. 3), were compared by a 2-way, repeated-measures ANOVA with Side (2 levels, left to right and right to left) and Modality (2 levels, nociceptive and tactile) as experimental factors.

3. Results

3.1. JND and PSS

JND and PSS values for pooled and individual data are reported in Table 1. Because data from the 'respond-to-first' and 'respond-to-second' response modes were not different,[2] they were combined and analysed together. The JND was larger when the participants' hands were crossed than it was when they were uncrossed, irrespective of the stimulus modality (Figs. 1 and 2). That is, there was a main effect of Position ($F(1,11) = 34.63$, $P < .001$), no main effect of Modality ($F(1,11) = 0.08$, $P = .78$), and no Position × Modality interaction ($F(1,11) = 2.54$, $P = .14$). Post-hoc comparisons, separate for each modality, confirmed the difference between uncrossed and crossed conditions, for both nociceptive stimuli (paired *t* test: $t(11) = 4.73$, $P = .001$) and tactile stimuli (paired *t* test: $t(11) = 5.53$, $P < .001$). Similar results were obtained when the same ANOVA was performed without including the ambidextrous participants (ie, only the main effect of Position was significant: $F(1,8) = 35.72$, $P < .001$).

Table 1
JND values and PSS.

Variable	JND, ms		PSS, ms	
	Pooled data	Individual data	Pooled data	Individual data
Nociceptive uncrossed	80	84 ± 46	−10	−16 ± 55
Nociceptive crossed	210	217 ± 101	−51	−43 ± 75
Nociceptive uncrossed vs crossed[a]	...	P < .001	...	NS
Tactile uncrossed	49	46 ± 21	−9	−17 ± 44
Tactile crossed	235	241 ± 34	−65	−58 ± 99
Tactile uncrossed vs crossed[a]	...	P = .001	...	NS

Data were obtained using the GCF. Individual data are expressed as mean ± standard deviation. JND, just noticeable difference; PSS, point of subjective simultaneity; GCF, Gaussian cumulative function.

[a] Post hoc comparisons.

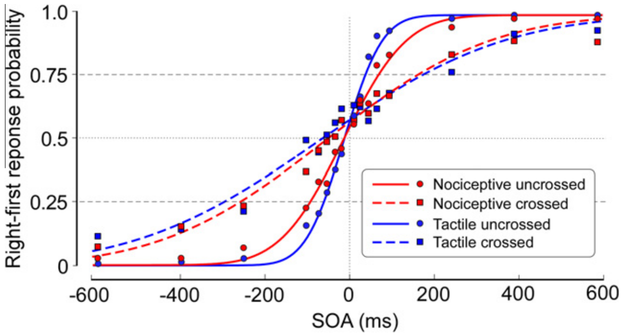

Fig. 1. Order judgement probabilities from pooled data, fitted with the Gaussian cumulative function (GCF). Data from the uncrossed (solid lines) and crossed (dashed lines) conditions, for nociception (red) and touch (blue). The x-axis indicates stimulus onset asynchronies (SOAs); the y-axis indicates the proportion of right-first responses. Negative SOAs indicate that the stimulus was delivered to the left hand first. The steepness of the curve reflects the performance, with steeper curves indicating better performance. Note that the ability to report correctly the order in which the 2 stimuli were delivered is reduced when participants crossed their hands over the body midline.

In contrast, the PSS was not affected by whether the participants' hands were uncrossed or crossed, either for nociceptive stimuli or for non-noxious tactile stimuli (Table 1). There was no main effect of Position ($F(1,11) = 1.58$, $P = .23$), no main effect of Modality ($F(1,11) = 0.74$, $P = .40$), and no Position × Modality interaction ($F(1,11) = 0.20$, $P = .66$). Similar results were obtained when the same ANOVA was performed without including the ambidextrous participants (all *F* values <1, all *P* values >.05).

3.2. Psychophysical curve fitting in crossed-hand position: GCF vs GFlipF

The goodness-of-fit coefficients of the GCF and GFlipF, for both pooled and individual data, are listed in Table 2. As expected, the GFlipF provided a significantly better fitting of individual crossed-hand data for both nociception and touch (main effect of Fitting: $F(1,11) = 29.81$, $P < .001$; no main effect of Modality: $F(1,11) = 0.43$, $P = .52$; and no Fitting × Modality interaction: $F(1,11) = 1.23$, $P = .29$).

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[2] To test whether the participants' performance in the experimental conditions was affected by the response mode (ie, respond-to-first vs respond-to-second), 2 ANOVAs, one on the JND and one on the PSS values, were also performed including Response mode, Modality, and Position as experimental factors. The main effect of Response mode and all the interactions involving this factor were not significant in either the JND or PSS ANOVAs (all F values $\leqslant 3.35$, all P values $\geqslant .10$). This finding indicates that the effects observed on the JND and PSS values did not differ between the 2 response modes.

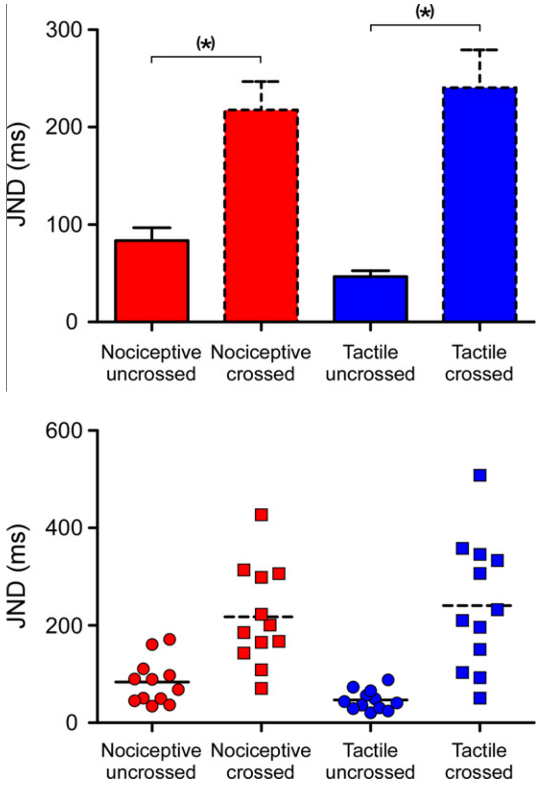

Fig. 2. Group-average (top) and single-subject (bottom) just noticeable difference (JND) values (ms) in the 4 conditions. Note that the JND is larger when the hands were crossed over the body midline (main effect of Position, $P < .001$), regardless of the stimulus modality (no significant Position × Modality interaction, $P = .14$).

3.3. Flipping

In the crossed-hand conditions, 9 out of 12 participants demonstrated a significant tendency to misreport (ie, invert) the order of nociceptive and tactile stimuli in at least one direction [28] (Table 3). Across the whole sample, the width of the time window during which there was a higher probability of judgement reversal (ie, the parameter σ_f), was not significantly different for nociception (169 ± 160 ms) and touch (182 ± 148 ms) (paired t test: $t(11) = 0.27$, $P = .78$). Furthermore, although the probability of inverting from left-first to right-first (A_l; nociception: 0.52 ± 0.26, touch: 0.62 ± 0.34) was on average greater than that of inverting from right-first to left-first (A_r; nociception: 0.46 ± 0.41, touch: 0.39 ± 0.29) for both nociception and touch, this difference was not statistically significant (no main effect of Side: $F(1,11) = 1.51$, $P = .24$; no main effect of Modality, $F(1,11) = 1.51$, $P = .24$; no Side × Modality interaction, $F(1,11) = 0.80$, $P = .39$). Similar results were obtained when the same ANOVA was performed without including the ambidextrous participants (all F values <1, all P values > .05).

Table 2
Goodness-of-fit coefficients (R^2).

Variable	GCF		GFlipF	
	Pooled data	Individual data	Pooled data	Individual data
Nociceptive uncrossed	0.99	0.94 (±0.05)	...	...
Nociceptive crossed	0.97	0.84 (±0.10)	0.98	0.88 (±0.06)
Tactile uncrossed	0.99	0.96 (±0.03)	...	...
Tactile crossed	0.96	0.80 (±0.12)	0.98	0.87 (±0.08)

Individual data are expressed as mean ± standard deviation. GCF, Gaussian cumulative function; GFlipF, Gaussian flip function.

4. Discussion

We tested the effect of crossing the hands on the temporal perception of both nociceptive and tactile stimuli. We obtained 2 main findings. First, there was a crossed-hands deficit for nociceptive stimuli. That is, crossing the hands over the midline significantly decreased the participants' ability to determine the order in which pairs of nociceptive stimuli were delivered to the hands. Second, such crossed-hands deficit had a similar temporal profile to that observed when delivering tactile stimuli. Taken together, these findings suggest that similar physiological mechanisms for integrating somatotopic and body-centred frames of reference underlie the ability to determine the location of both nociceptive and tactile stimuli.

4.1. Nociceptive-specific stimuli for TOJ

Many studies have used TOJ tasks while the hands are crossed over the midline to investigate the respective contribution of different frames of reference in localising tactile stimuli in space [11,24,26–28]. The question as to whether or not the nociceptive system engages similar mechanisms to localise stimuli has not been addressed, because of the difficulty in delivering, in rapid succession, pairs of nociceptive stimuli which are both selective (ie, that do not coactivate Aβ fibres) and sufficiently transient. We achieved this by using low-intensity IES, which has been demonstrated to selectively activate skin nociceptors. When applied with a stimulus intensity not above twice the perceptual threshold, the

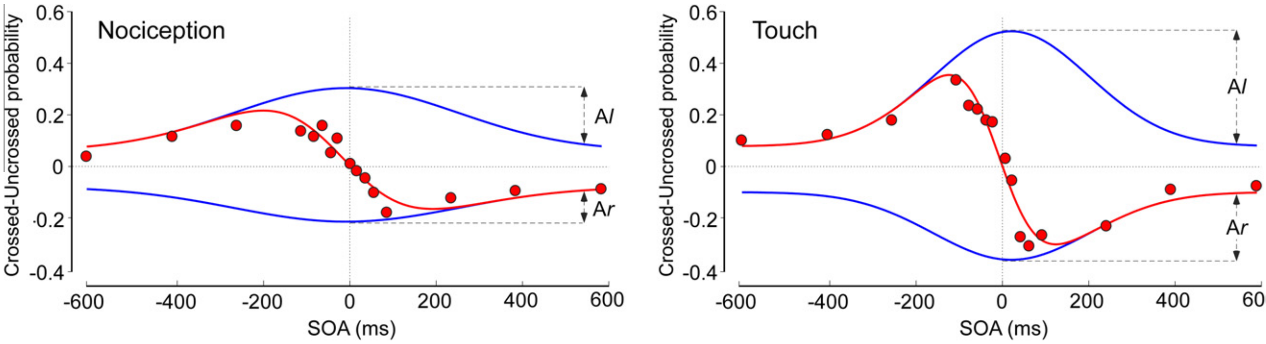

Fig. 3. Group-level difference (red lines) between the order judgement probabilities obtained in the crossed and the uncrossed conditions for nociception (left) and touch (right). This difference is calculated by subtracting the GCF (estimated from the data of uncrossed conditions) from the GFlipF (estimated from the data of crossed conditions). The upwards and downwards Gaussian curves (blue) correspond to the functions f_l and f_r in the GFlipF (Appendix A).

Table 3
Probability of inversion from left-first to right-first (A_l) and from right-first to left-first (A_r).

Subject No.	A_l		A_r	
	Nociceptive crossed	Tactile crossed	Nociceptive crossed	Tactile crossed
1	0.17	0.81	0.38	0.94
2	0.53	0.95	0.11	0
3	0.46	0	0	0.55
4	0.27	0.70	0.32	0.44
5	0.58	0.35	0.23	0.75
6	0.70	0.60	0.1	0
7	0	0.37	1	0.34
8	0.66	0.41	0.25	0.36
9	0.68	1	1	0.63
10	0.66	0.32	1	0.28
11	0.94	1	0.01	0.11
12	0.54	1	1	0.31
Mean ± standard deviation	0.52 ± 0.26	0.62 ± 0.34	0.46 ± 0.41	0.39 ± 0.29

electric current generated by the IES is spatially restricted to the epidermal layers and thus does not activate Aβ fibres. Crucially, as IES bypasses receptor transduction and directly activates Aδ fibres [20], the afferent volley produced by IES is highly synchronous and reproducible; it is thus optimal for exploring TOJ of pairs of stimuli delivered in rapid succession at different locations.

4.2. Crossed-hands deficit for nociceptive stimuli

The crossed-hands deficit has been repeatedly described when TOJs are performed by using tactile but not visual stimuli [28]. We have now demonstrated that nociceptive stimuli are also coded both in somatotopic and body-centred frames of reference. As, for example, the right hand commonly occupies the right side of space, stimuli delivered on the right hand automatically activate both the cortical area representing the right hand and the multimodal areas representing the right side of space [5,28]. When the hands are crossed over the midline, the participants' ability to discriminate the order in which the hands are stimulated at short intervals is impaired, possibly because the second stimulus is processed while the spatial location of the first stimulus is still being determined according to the uncommon position of the hands [28].

Converging evidence from human and non-human studies indicates that frontoparietal cortical areas, such as the premotor cortex and the ventral intraparietal area and its human homologous, are responsible for mapping tactile inputs into body-centred coordinates. Furthermore, these associative areas are responsible for integrating multimodal inputs within a body-centred frame of reference [13–15]. We recently demonstrated that crossing the hands over the midline reduces the amplitude of the N2-P2 biphasic wave elicited by either nociceptive (Aδ) or non-nociceptive (Aβ) input [5]. These waves largely reflect the activity of multimodal brain areas [19]. In contrast, crossing the hands does not affect the amplitude of the earlier N1 wave, which reflects the activity of somatosensory-specific brain areas [5,19]. This evidence, together with the current result of a crossed-hands deficit for nociceptive stimuli, suggests that multimodal areas responsible for encoding the location of somatosensory stimuli in space are common for touch and pain.

Recent evidence from clinical studies also supports that a body-centred frame of reference is used to localise nociceptive stimuli in space. For example, Liu et al. [12] reported that, similarly to what is observed in other modalities (ie, vision and touch), patients with ischemic lesions in the right hemisphere may not report the occurrence of nociceptive stimuli applied on the contralesional hand when presented either in isolation (nociceptive neglect) or simultaneously with an ipsilesional stimulus (nociceptive extinction). Moreover, these patients may misreport the location of stimuli applied to the contralesional hand as if they were applied to the ipsilesional hand (nociceptive allesthesia). These results suggest that an intact representation of external space with reference to the subject's body midline is important for awareness of nociceptive stimuli and their correct localisation [10].

The importance of understanding how the nociceptive system engages somatotopic and spatial frames of reference is evidenced by recent findings in people with complex regional pain syndrome (CRPS). In a TOJ task using tactile stimuli, patients with CRPS prioritized stimuli applied to the unaffected limb over those applied to the affected limb when their hands were uncrossed, but this effect was reversed when their hands were crossed over the midline [16]. That is, patients prioritized stimuli delivered to whichever hand was on the unaffected side of the body midline, thus suggesting the involvement of a space-based rather than an anatomically-based representation in determining a number of symptoms in these patients [17]. This idea is further supported by the recent discovery of a space-based disruption of tactile processing in patients with low back pain [18].

What could be the functional significance of the observation that also nociceptive stimuli are mapped into a body-centred frame of reference? Although defensive withdrawal responses are mediated by subcortical circuits, somatotopic representations alone would be insufficient to localise potentially dangerous stimuli, because the body can assume different postures. For these reasons, the pattern of a motor withdrawal response is finely adjusted in a purposeful manner, according to a body-centred frame of reference [23]. Furthermore, the mapping of nociceptive stimuli into external coordinates is also critical to integrate them with visual and auditory inputs in order to respond with purposeful and non-stereotyped behaviours to potentially aversive multimodal stimuli in the environment.

4.3. Temporal profile of the crossed-hands deficit in nociception and touch

We found that the crossed-hands deficit observed when delivering nociceptive stimuli had a similar temporal profile to that observed when delivering tactile stimuli (no significant Modality × Position interaction; Figs. 1 and 2). Crucially, we observed that a high proportion of subjects (75% for nociception and 75% for touch) demonstrated a significant tendency to misreport (i.e., invert) the order of the 2 stimuli. This is a crucial finding, because it strongly suggests that, when the hands are crossed, the stimulus (delivered, for example, on the right hand) is first mapped on the right hand area of S1 and on the areas encoding the right side of space (ie, those areas usually coactivated when a stimulus is delivered on the right hand in common, uncrossed posture). Only after a few hundred ms, the stimulus is mapped in the correct side of space (left, in this example). Such inversion is thought to reflect an automatic mapping of the stimulus to the side of space where the stimulated hand is usually located—the ipsilateral side of space [25]. Indeed, if the second stimulus is delivered before the first stimulus is correctly mapped in the side of space where the stimulated hand is placed, then the order of stimuli is misreported [28]. This proposal has been confirmed by an elegant paradigm that characterised the time course of such correction, which starts not earlier than 60 ms and is completed between 180 to 360 ms after stimulus presentation [2].

The current findings provide evidence that both the sequence and the time course of the cortical events that determine the perception of nociceptive stimuli are similar to those involved in perceiving tactile stimuli, even when the hands are crossed over the midline. This result is in line with the observation that the areas encoding stimuli in body-centred coordinates are eminently multimodal [6,13], and only the multimodal components of the event–related potentials elicited by both Aβ and Aδ inputs [19] are significantly modulated when hands are crossed over the midline [5].

4.4. Side bias in TOJ

The SOA at which the 2 stimuli were perceived as simultaneous (ie, PSS) was close to zero for both modalities and both postures, which indicates that the participants were not prioritizing stimuli delivered at one side or the other. In contrast to what observed when measuring the JND, crossing the hands over the midline did not affect the PSS, as also reported in previous studies using tactile stimuli [21,24]. Such dissociation in the effect of crossing the hands on PSS and JND is compatible with the notion that TOJ of somatosensory stimuli involves 2 separate mechanisms, one responsible for determining whether 2 stimuli are simultaneous or sequential, and the other responsible for resolving their order [9].

4.5. Conclusion

Our results uphold the hypothesis that the crossed-hands deficit is present when judging the temporal order of not only tactile stimuli, but also purely nociceptive stimuli. Our results also demonstrate that the temporal profile of such deficit is similar to that observed for tactile stimuli. These results offer compelling evidence that similar physiological mechanisms for integrating somatotopic and body-centred frames of reference underlie the ability to determine the location of nociceptive and tactile stimuli in space.

Conflict of interest statement

The authors report no conflict of interest.

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Appendix A

The order judgement probabilities in the uncrossed conditions (p_u) were fitted by a Gaussian cumulative function (GCF):

$$p_u(t) = (p_{max} - p_{min}) \int_{-\infty}^{t} \frac{1}{\sqrt{2\pi\sigma_u}} e^{\frac{-(\tau-d_u)^2}{2\sigma_2^2}} d\tau + p_{min}$$

where t indicates the stimulus onset asynchrony (SOA); p_{max} and p_{min} indicate the upper and lower asymptotes of the judgement probability, respectively; σ_u represents the time constant; and d_u represents the size of the horizontal transition. This equation was also used to fit the order judgement probabilities in the crossed condition to determine the just noticeable difference (JND) and the point of subjective simultaneity (PSS) values.

The order judgement probabilities in the crossed conditions (p_c) were also fitted using a Gaussian flip function (GFlipF):

$$p_c(t) = f_l(t)\{1 - p_u(t)\} + \{1 - f_r(t)\}p_u(t)$$

where f_l indicates the flip probability of judgement from left-first to right-first and f_r indicates the flip probability of judgement from right-first to left-first. The f_l and f_r values were calculated by the following equations:

$$f_l(t) = A_l e \frac{-(t-d)^2}{2\sigma_f^2} + c$$

$$f_r(t) = A_r e \frac{-(t-d)^2}{2\sigma_f^2} + c$$

where A_{l} and A_r (ie, the peak amplitudes of the Gaussian functions; Fig. 2) reflect the probability of inversion from left-first to right-first and from right-first to left-first, respectively; d represents the size of the horizontal transition; σ_f represents the width of the time window of the flip; and c is a constant.

References

[1] Andersen RA. Multimodal integration for the representation of space in the posterior parietal cortex. Philos Trans R Soc Lond B Biol Sci 1997;352:1421–8.
[2] Azanon E, Soto-Faraco S. Changing reference frames during the encoding of tactile events. Curr Biol 2008;18:1044–9.
[3] Cadieux ML, Barnett-Cowan M, Shore DI. Crossing the hands is more confusing for females than males. Exp Brain Res 2010;204:431–46.
[4] Gallace A, Soto-Faraco S, Dalton P, Kreukniet B, Spence C. Response requirements modulate tactile spatial congruency effects. Exp Brain Res 2008;191:171–86.
[5] Gallace A, Torta DM, Moseley GL, Iannetti GD. The analgesic effect of crossing the arms. PAIN® 2001;152:1418–23.
[6] Graziano MS, Gross CG. The representation of extrapersonal space. A possible role for bimodal, visual–tactile neurons. In: Gazzaniga MS, editor. The cognitive neurosciences. Cambridge, MA: MIT Press; 1995. p. 1021–34.
[7] Inui K, Kakigi R. Pain perception in humans: use of intraepidermal electrical stimulation. J Neurol Neurosurg Psychiatry 2012;83:551–6.
[8] Inui K, Tran TD, Qiu Y, Wang X, Hoshiyama M, Kakigi R. Pain-related magnetic fields evoked by intra-epidermal electrical stimulation in humans. Clin Neurophysiol 2002;113:298–304.
[9] Jaskowski P. Two-stage model for order discrimination. Percept Psychophys 1991;50:76–82.
[10] Kitazawa S. Where conscious sensation takes place. Conscious Cogn 2002;11:475–7.
[11] Kobor I, Furedi L, Kovacs G, Spence C, Vidnyanszky Z. Back-to-front: improved tactile discrimination performance in the space you cannot see. Neurosci Lett 2006;400:163–7.
[12] Liu CC, Veldhuijzen DS, Ohara S, Winberry J, Greenspan JD, Lenz FA. Spatial attention to thermal pain stimuli in subjects with visual spatial hemi-neglect: extinction, mislocalization and misidentification of stimulus modality. PAIN® 2011;152:498–506.
[13] Lloyd DM, Shore DI, Spence C, Calvert GA. Multisensory representation of limb position in human premotor cortex. Nat Neurosci 2003;6:17–8.
[14] Maravita A, Spence C, Driver J. Multisensory integration and the body schema: close to hand and within reach. Curr Biol 2003;13:R531–9.
[15] Medina J, Coslett HB. From maps to form to space. Touch and the body schema. Neuropsychologia 2010;48:645–54.
[16] Moseley GL, Gallace A, Spence C. Space-based, but not arm-based, shift in tactile processing in complex regional pain syndrome and its relationship to cooling of the affected limb. Brain 2009;132:3142–51.
[17] Moseley GL, Gallace A, Spence C. Bodily illusions in health and disease: physiological and clinical perspectives and the concept of a cortical 'body matrix'. Neurosci Biobehav Rev 2012;36:34–46.
[18] Moseley GL, Gallagher L, Gallace A. Neglect-like tactile dysfunction in chronic back pain. Neurology 2012;79:327–32.
[19] Mouraux A, Iannetti GD. Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. J Neurophysiol 2009;101:3258–69.
[20] Mouraux A, Iannetti GD, Plaghki L. Low intensity intra-epidermal electrical stimulation can activate A delta-nociceptors selectively. PAIN® 2010;150:199–207.
[21] Nicholls ME, Lindell AK. A left hemisphere, but not right hemispace, advantage for tactual simultaneity judgments. Percept Psychophys 2000;62:717–25.
[22] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97–113.
[23] Pearson K, Gordon J. Spinal reflexes. In: Jessell TM, Schwartz JH, Kandel ER, editors. Principles of neural science. Amsterdam: Elsevier Science; 2000. p. 713–36.
[24] Radomsky AS, Rachman S, Thordarson DS, McIsaac HK, Teachman BA. The claustrophobia questionnaire. J Anxiety Disord 2001;15:287–97.
[25] Roder B, Rosler F, Spence C. Early vision impairs tactile perception in the blind. Curr Biol 2004;14:121–4.
[26] Shore DI, Spry E, Spence C. Confusing the mind by crossing the hands. Brain Res Cogn Brain Res 2002;14:153–63.
[27] Wada M, Yamamoto S, Kitazawa S. Effects of handedness on tactile temporal order judgment. Neuropsychologia 2004;42:1887–95.
[28] Yamamoto S, Kitazawa S. Reversal of subjective temporal order due to arm crossing. Nat Neurosci 2001;4:759–65.