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The analgesic effect of crossing the arms

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ABSTRACT

The ability to determine precisely the location of sensory stimuli is fundamental to how we interact with the world; indeed, to our survival. Crossing the hands over the body midline impairs this ability to localize tactile stimuli. We hypothesized that crossing the arms would modulate the intensity of pain evoked by noxious stimulation of the hand. In two separate experiments, we show (1) that the intensity of both laser-evoked painful sensations and electrically-evoked nonpainful sensations were decreased when the arms were crossed over the midline, and (2) that these effects were associated with changes in the multimodal cortical processing of somatosensory information. Critically, there was no change in the somatosensory-specific cortical processing of somatosensory information. Besides studies showing relief of phantom limb pain using mirrors, this is the first evidence that impeding the processes by which the brain localises a noxious stimulus can reduce pain, and that this effect reflects modulation of multimodal neural activities. By showing that the neural mechanisms by which pain emerges from nociception represent a possible target for analgesia, we raise the possibility of novel approaches to the treatment of painful clinical conditions.

1. Introduction

Pain reduces tissue damage by motivating escape [12]. In order to be fully effective for survival, the ability to localize where a noxious stimulus occurs must be as accurate as possible [54]. Furthermore, the processing of the spatial information of a sensory input is one of the important requisites for it reaching awareness, as impeding the processing of a stimulus' location often impedes also the *perception* of that stimulus [17,18]. This raises the possibility that disrupting the processes by which the location of a sensory stimulus is determined will reduce the perceived intensity of that stimulus.

Remarkably, disrupting the very processes by which nociceptive input emerges into awareness [27] by acting upon its correct spatial localization has not, until now, been targeted as a method of reducing pain in healthy volunteers, although the mislocalization of noxious stimuli by a mirror has been shown to result in reduction of pain in patients with phantom limb [47]. In contrast, there have been successful attempts to impede awareness of nociceptive stimuli by acting upon a person's state of consciousness or attention [26,35].

The ability to localise tactile inputs is impaired when hands are crossed over the body midline [1]. For example, when 2 sequential stimuli are presented, one on each hand, crossing the hands over the body midline reduces our ability to determine which hand was stimulated first [15,53]. This "crossed-hands deficit" is thought to occur because of a mismatch between the location of the stimulus within an anatomical (or somatotopical) frame of reference and the location of the stimulus within a space-based frame of reference [4,16,53]. Indeed, to localize correctly sensory inputs in the environment, most of the somatosensory experience must be referred to spatial locations defined according to nonsomatotopical frames of reference [20,42,45]. It is thought that integration of information between these 2 frames of reference probably occurs in *multimodal* brain areas, that is, areas responding to stimuli of different sensory modalities [2].

So far, crossed-hands studies have not explored the intensity of perception or the neural activity elicited by somatosensory stimuli delivered to the hands. Given that (1) crossing the hands over the body midline impairs the ability to localise tactile stimuli [1]; (2) localization of tactile stimuli is an important requisite for awareness (eg, [18]); and (3) multimodal brain areas (eg, associational and limbic areas that respond to stimuli belonging to different sensory modalities [2,32]) have been hypothesized to play a more important role in awareness of both tactile [17] and noxious [27] stimuli than somatosensory-specific brain areas do, we hypothesized that

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crossing the arms would impede multimodal processing of somatosensory stimuli delivered to the hands, and thereby decrease the intensity of both painful and tactile sensations. As multimodal processing of somatosensory stimuli is reflected in the late components of the event-related potentials (ERPs) elicited by somatosensory stimuli [40], we would expect a stronger modulation of late rather than early ERP components when the hands are crossed over the midline.

To test these 2 hypotheses, we investigated the intensity of the sensations (*Experiment 1*) and the brain activity (*Experiment 2*) evoked by nonnociceptive electrical stimuli and nociceptive laser stimuli delivered to the hands, while the subject's arms were either crossed or not crossed over the body midline.

2. Material and methods

2.1. Participants

Eight right-handed healthy subjects (4 women, mean age 28 ± 4.7 years) took part in Experiment 1. Twelve right-handed healthy subjects (6 women, mean age 31 ± 10.6 years) took part in Experiment 2. All participants gave their written informed consent. This study conformed to the standards required by the Declaration of Helsinki and was approved by the institutional ethics committee.

2.2. Procedure

Participants were comfortably seated in a silent, temperature-controlled room, and wore protective laser-proof goggles. Earplugs and headphones were also worn in order to remove any possibly auditory cue arising from the operation of the devices. Two large wooden screens placed in front of the participants occluded their view of both their arms and the experimenter. A fixation point was placed 30 cm in front of, and 30° below their eyes. Before the beginning of the experiments participants were familiarised with the sensory stimulation (5–10 stimuli of each modality). During the experiment the participants were asked to keep their arms either uncrossed or crossed over the midline. The distance between the hands was the same (40 cm) in the 2 conditions. Crossed and uncrossed blocks were run separately (see below for further details).

2.2.1. Nonnociceptive somatosensory stimuli

Nonnociceptive somatosensory stimuli consisted of constant current square-wave pulses (1-ms duration; DS7A, Digitimer, Hertfordshire, UK) delivered through 2 electrodes (0.5 cm diameter, 2 cm interelectrode distance) placed at the wrist, over the superficial radial nerve. Stimulus intensity was adjusted to elicit a clear, nonpainful paresthesia. Electrical stimuli were always delivered at an intensity that was above the threshold of Aβ fibres (which convey nonnociceptive tactile information) but below the threshold of nociceptive Aδ and C fibres [9]. In all experiments, electrical stimuli were never reported as painful.

2.2.2. Nociceptive somatosensory stimuli

Nociceptive somatosensory stimuli consisted of 4-ms pulses of radiant heat generated by an infrared neodymium yttrium aluminium perovskite (Nd:YAP) laser (wavelength 1.34 μm, El.En. Group, Florence, Italy). Beam diameter at target site was $\sim$8 mm. Laser stimuli were delivered to the sensory territory of the superficial radial nerve. Stimulus energy was initially adjusted to elicit a clear painful pinprick sensation, related to the selective activation of Aδ skin nociceptors, thus solving the previously problematic issue of the co-activation of nonnociceptive afferents [7,10]. To prevent nociceptor fatigue or sensitization, the laser target was displaced after each pulse.

Both experiments involved 8 blocks of 30 stimuli each (interstimulus interval randomised between 8 and 12 seconds). Fifteen stimuli were delivered to each hand in pseudorandom counterbalanced order. The maximum number of consecutive stimuli delivered to the same hand was 3. Both stimulus modality (nonnociceptive and nociceptive) and hand position (crossed or uncrossed) were the same within each block. There were 2 blocks each of "nonnociceptive crossed," "nonnociceptive uncrossed," "nociceptive crossed," and "nociceptive uncrossed." The order of blocks was balanced across participants.

2.2.3. Experiment 1

In *Experiment 1*, 3 energies of both nonnoxious and noxious stimulations were determined using two, 0–100 numerical rating scales, one for the sensation elicited by laser stimuli and one for the sensation elicited by electrical stimuli. The anchors of the scale used to rate the intensity of perception elicited by laser stimuli were "no pinprick sensation" (0) and "the strongest pinprick sensation imaginable" (100). When rating laser stimuli, participants were explicitly instructed to rate 0 in response to a nonpricking (eg, nonpainful warm) sensation. The anchors of the scale used to rate the intensity of perception elicited by electrical stimuli were "no electrical sensation" (0) and "the strongest electrical sensation imaginable" (100). "Low," "medium," and "high" energies, corresponding to ratings of 30, 50, and 70, were 4.1 ± 1.7 mA, 6.8 ± 2.3 mA, and 10.2 ± 3.4 mA for electrical and 2 J, 2.5 J, and 3 J for laser stimulation, respectively. At these energies, Nd: YAP laser pulses consistently elicit painful sensations (eg, [21]). Ten stimuli of each energy were delivered in pseudorandom counterbalanced order. The maximum number of consecutive stimuli of the same energy was 3. Participants rated the perceived intensity of each stimulus.

2.2.4. Experiment 2

In *Experiment 2*, one stimulus energy (11.8 ± 4.0 mA for electrical and 3.0 ± 0.5 J for laser) was used. The electroencephalogram was recorded using 21 scalp electrodes placed according to the International 10-20 system. The nose was used as common reference. Signals were amplified and digitized (sampling rate 1024 Hz; resolution = 0.195 $\mu V\ digit^{-1}$; System Plus, Micromed, Italy), segmented into 1-second epochs (-200 to +800 ms relative to stimulus onset) and band-pass filtered (1–30 Hz). After baseline correction (reference interval -200 to 0 ms), artefacts due to eye blinks or movements were subtracted using a validated method [23]. Epochs exceeding ± 100 μV amplitude (ie, likely to be contaminated by artefact) were rejected. They were 0.8 ± 1.6% of the total number of epochs. Separate average ERP waveforms time-locked to stimulus onset were computed for each participant, according to stimulus modality (nonnociceptive or nociceptive) and hand position (crossed or uncrossed). Baseline-to-peak amplitude of the N1 wave, which represents an early stage of sensory processing and reflects the somatosensory-specific afferent input and its somatotopical arrangement, and peak-to-peak amplitude of the N2-P2 wave, which represents a later stage of processing and mostly reflects multimodal neural activities [27,40,50], were measured. The labels N1 and N2-P2 for the ERPs elicited by both nonnociceptive and nociceptive stimuli were chosen according to Treede et al [49]. Analyses were conducted using Letswave [39] and Matlab (MathWorks, Natick, MA, USA).

3. Results

3.1. Experiment 1

For each of the 3 energies used, laser stimuli elicited a clear pinprick pain in all participants, related to the activation of Aδ fibres

[7]. Ratings of perceived intensity are reported in Table 1. A 3-way analysis of variance ("stimulus modality" [nonnociceptive or nociceptive] × "arm position" [crossed or uncrossed] × "stimulus energy" [low, medium, or high]) revealed that crossing the arms reduced the intensity of the sensation evoked by the stimuli, regardless of their sensory modality and of the energy of the applied stimulus (main effect of "arm position": F(1, 6) = 7.54, *P* = 0.03; "stimulus modality" × "arm position" interaction: F(1, 6) = 0.55, *P* = 0.48; "stimulus energy" × "arm position" interaction: F(1, 6) = 0.07, *P* = 0.91). That is, crossing the arms decreased the intensity of the sensations elicited by both nonnoxious and noxious stimuli (Fig. 1).

3.2. Experiment 2

Amplitudes of ERPs are reported in Table 2. A 2-way analysis of variance ("stimulus modality" [nonnociceptive or nociceptive] × "arm position" [crossed or uncrossed]) revealed that crossing the arms over the midline reduced the amplitude of the N2-P2 wave, regardless of stimulus modality (main effect of "arm position": F(1, 11) = 9.27, *P* = 0.01; "stimulus modality" × "arm position" interaction: F(1, 11) = 0.04, *P* = 0.81). In contrast, crossing the arms did not reduce the amplitude of the N1 wave for either stimulus modality (main effect of "arm position": F(1, 11) = 1.43, *P* = 0.26; "stimulus modality" × "arm position" interaction: F(1, 11) = 0.16, *P* = 0.68), which shows no effect of crossing the arms on somatosensory-specific processing (Fig. 2).

4. Discussion

We hypothesized that crossing the arms would impede multimodal processing of somatosensory stimuli delivered to the hands, and thereby decrease pain and touch. Our results clearly uphold this hypothesis – crossing the arms reduced the perceived intensity of both laser-evoked painful sensations and electrically evoked nonpainful sensations, as evidenced by the behavioural data (Experiment 1), and selectively disrupted multimodal processing of both nonnociceptive and nociceptive somatosensory stimuli, as evidenced by the decreased amplitude of the N2-P2 wave (Experiment 2). The clear dissociation between the absence of N1 wave modulation and the presence of N2-P2 wave modulation indicates a clear effect of crossing the arms on multimodal, but not somatosensory-specific, neural processing.

One possible explanation for this effect relies on the cognitive costs associated with realigning neural representations based on different spatial frames of reference. When we cross our hands, the conflict between the sensory inputs represented in different frames of reference requires the brain to realign somatosensory coordinates to spatial coordinates, which has a cost in terms of processing resources [53]. The modulation of the neural components reflected in the N2-P2 peaks is likely to represent the neural correlate of this cost, while the reduced intensity of the sensations elicited by both nonnoxious and noxious stimuli represents its behavioural counterpart.

Table 1
Experiment 1: behavioural results.

	Hands uncrossed	Hands crossed
Electrical stimulation[a]		
Energy 1	18.4 ± 10	17.2 ± 10
Energy 2	32.8 ± 9	31 ± 9
Energy 3	45.3 ± 13	43.5 ± 12
Laser stimulation[b]		
Energy 1	20.3 ± 8	17.8 ± 8
Energy 2	48.2 ± 9	44.6 ± 9
Energy 3	60.6 ± 8	57.7 ± 9

Values are expressed as mean ± SD. Statistical comparisons are reported in the text.

[a] Values represent intensity of perception according to a 0–100 numerical scale, where 0 represents "no sensation" and 100 "the strongest electrical sensation imaginable.".

[b] Values represent intensity of perception according to a 0-100 numerical scale, where 0 represents "no sensation" and 100 "the strongest pinprick sensation imaginable.".

A second possible explanation is related to the fact that, when the arms are held in an uncommon posture (ie, when they are crossed), the relevance of the stimuli delivered on the hands might be reduced. Indeed, it has been repeatedly reported that the attentional context in which the eliciting stimulus is presented alters the magnitude of the N2 and P2 peaks of somatosensory ERPs, even if the intensity of the afferent input is constant (eg, [21,27–29]).

It has been suggested that nonnociceptive somatosensory information is initially processed in a somatotopic frame of reference, and needs to be later transformed into a more abstract frame of reference to become available for conscious processing ([24,53]; though see [16]). Thus, the crossed-hand deficit has been so far interpreted in terms of the process of progressive "recoding" of sensory information throughout different spatial maps [4].

However, it is well known that the several cortical maps in primate sensory systems are activated both in series and in parallel, and that they are heavily interconnected [38]. There is also evidence of parallel processing in the human somatosensory system (eg, [25,33]). For example, after ischemic injury to one entire primary somatosensory area, patients can be completely unaware of tactile stimuli delivered to the contralateral body side, but still able to point correctly to where they occurred [6,42,51]. This empirical evidence of a somatosensory equivalent of blindsight [44,52] suggests that spatial information regarding tactile stimuli can be processed and integrated with motor commands, without primary somatosensory cortex involvement, possibly by direct anatomical connections between the lateral posterior thalamic nuclei and the posterior parietal cortex [6,18,22,33].

On that basis, an alternative possibility can be suggested: that tactile stimuli, rather than being sequentially converted from one frame of reference to another, are always mapped both in a somatosensory and in a space-based representation, and that this dual mapping happens before conscious judgments are made. Obviously, the strength of activation of each map might be modulated by a number of parameters (such as the availability of visual and proprioceptive information, as well as the immediate relevance of the task; eg, [16]). For example, seeing the arms might enhance the neural representation of sensory stimuli in the space-based map. Thus, the modulation of the perceived intensity of a stimulus delivered to the hands while they are crossed over the midline might not be the consequence of the need to remap the input from the somatosensory to the spaced-based map, but of a lack of correspondence between the "expected" neural activities elicited by the stimulus in these 2 maps.

In everyday life, the right and left hands manipulate objects and are exposed to somatosensory stimuli that are more often present on the right or on the left side of space, respectively. For example, stimuli activating mechanoreceptors on the left hand occur much more often on the left side of the body midline. Thus, the representation of the hand in the somatotopic map is often activated together with the representation of the left side of space in the space-based map (Fig. 3). Consequently, it is likely that, among the extensive connections between these 2 maps [17,18], those between the regions more often receiving a sensory input resulting in a simultaneous pattern of activity (eg, the left hand area in the somatosensory map and the left side area of the space-based map) are likely to display increased synaptic strengths. When our hands are uncrossed, the match between the 2 frames of reference makes the processing of sensory stimuli delivered to the hands

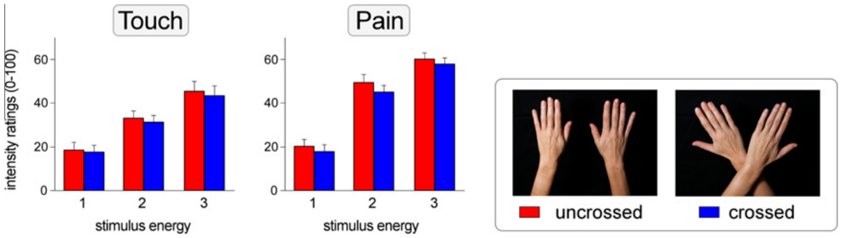

Fig. 1. Behavioural results (*Experiment 1*). The left panel represents the intensity of the sensations evoked by nonnoxious stimuli (left graph) and noxious stimuli (right graph), which were delivered to the hands while the arms were either crossed (in blue) or uncrossed (in red). Three energies of both types of somatosensory stimuli were used. Crossing the arms significantly reduced the intensity of the sensation evoked by the stimuli, regardless of their sensory modality (main effect of "arm position": $P = 0.03$; "stimulus modality" × "arm position" interaction: $P = 0.48$).

Table 2
Experiment 2: event-related potential (ERP) results.

	Hands uncrossed	Hands crossed
Electrical stimulation		
N1 wave	−3.8 ± 4.9	−4.5 ± 4.8
N2-P2 wave	34.0 ± 14.5	31.5 ± 13.9
Laser stimulation		
N1 wave	−4.2 ± 3.6	−4.8 ± 2.6
N2-P2 wave	36.7 ± 19.3	33.2 ± 17.5

Values represent peak amplitude in μV (mean ± SD). Statistical comparisons are reported in the text.

highly effective in enhancing the sensory signal due to the privileged synaptic connections between the corresponding areas of the 2 maps (Fig. 3, left panel). In contrast, when we hold an uncommon body posture, such as crossing the hands over the midline, these privileged synaptic connections are not engaged (Fig. 3, right panel). Therefore, although the correct localisation of stimuli in space is still possible, the enhancement of the sensory signal is impeded, which might result in decreased intensity of perception. Interestingly, it has been recently shown that performance in temporal order judgment tasks, which are commonly used to investigate the reference frames involved in the localisation of somatosensory inputs (as well as the temporal aspects of our awareness), is abnormal when the hands are crossed over the midline [53], but only in children older than ~5 years [41]. This suggests that, ontogenetically, somatosensory events are referred to nonsomatotopical frames of references only after the development of space-based maps. Before the development of those maps, our ability to localise somatosensory stimuli relies completely on anatomical frames of reference.

The magnitude of early components of the response elicited by somatosensory stimuli (eg, the N1 wave of laser-evoked

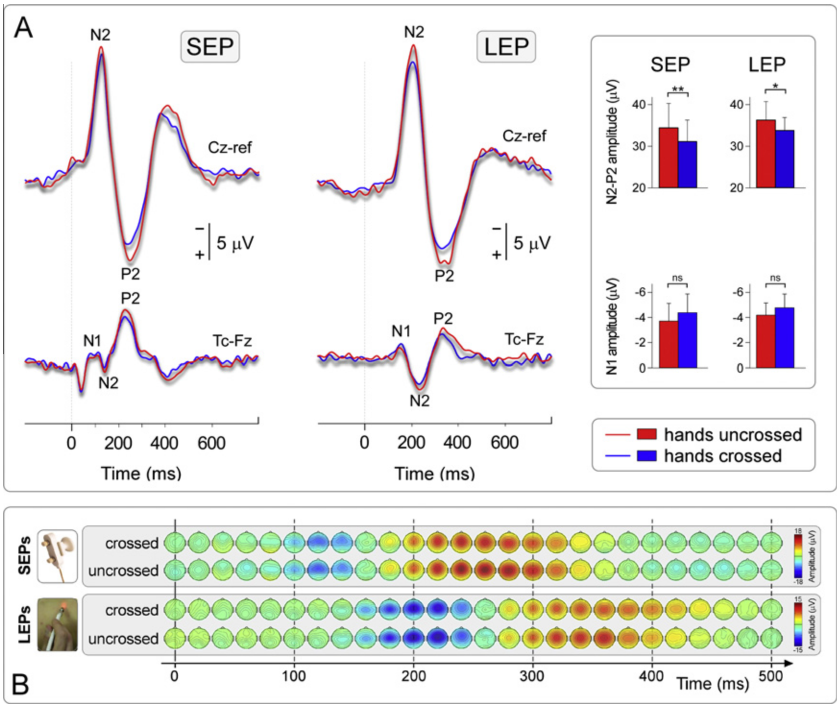

Fig. 2. Electrophysiological results (*Experiment 2*). (A) Grand-average waveforms showing the N1 and N2-P2 waves of somatosensory-evoked potentials elicited by nonnociceptive electrical stimuli (SEPs, left panel) and nociceptive laser stimuli (LEPs, right panel) delivered to the hand dorsum while arms were crossed (blue waveforms) and uncrossed (red waveforms). Crossing the arms significantly reduced the peak amplitude of the N2-P2 wave, regardless of stimulus modality (main effect of "arm position": $P = 0.01$; "arm position" × "stimulus modality" interaction: $P = 0.81$). In contrast, crossing the arms did not reduce the peak amplitude of the N1 wave for either stimulus modality (main effect of "arm position": $P = 0.26$, "arm position" × "stimulus modality" interaction: $P = 0.68$). The clear dissociation between the absence of N1 wave modulation and the presence of a strong N2-P2 wave modulation indicates that the analgesic effect imparted by crossing the arms involves multimodal, but not somatosensory-specific, processing. (B) Group-level scalp distribution of SEPs (top panel) and LEPs (bottom panel) elicited by stimulation of the hand dorsum while the arms were crossed (top row in each panel) and uncrossed (bottom row in each panel). Scalp maps are displayed at 20-ms intervals, from stimulus onset to 500 ms poststimulus.

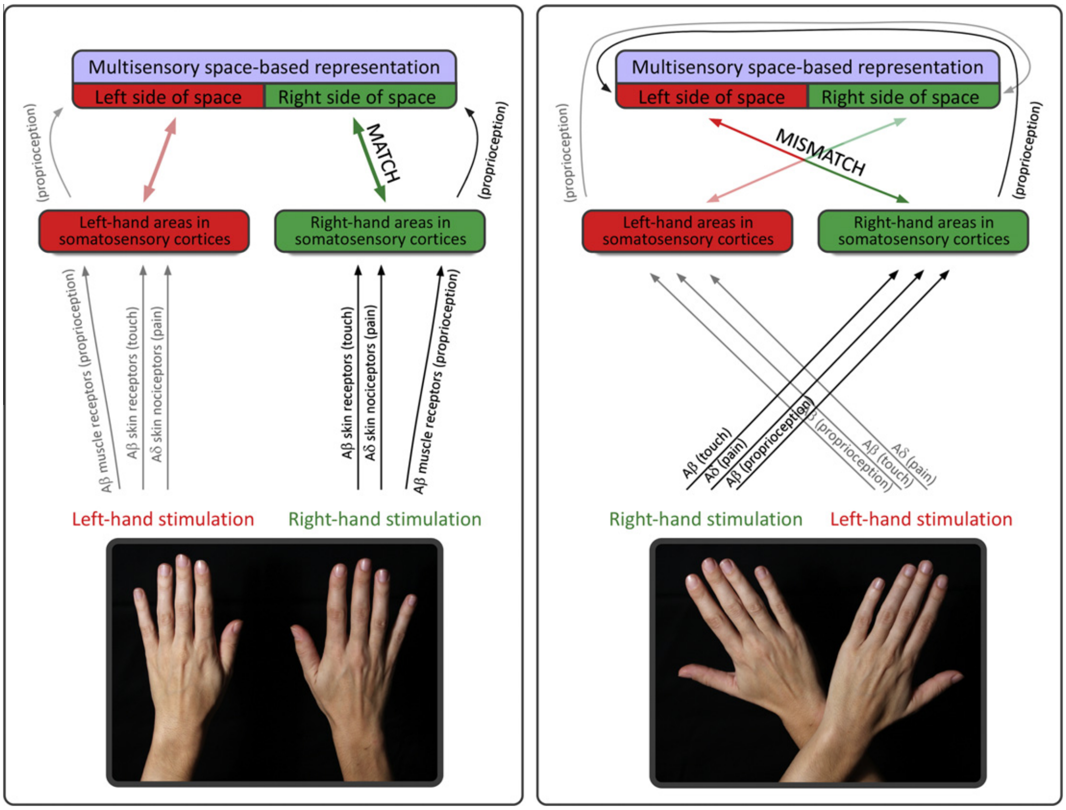

Fig. 3. A putative neurocognitive model supporting the presented findings. Tactile, nociceptive, and proprioceptive information arising from, for example, the right hand (black arrows), reaches the corresponding areas in the somatosensory cortices. When the hands are uncrossed (left panel), these inputs also activate multisensory areas mapping the right side of the external space, with reference to the body midline. Thus, stimulation of each hand results in a match between somatosensory and space-based representations (thick, green double arrow). When the hands are crossed (right panel), somatosensory information arising from, for example, the right hand (black arrows), reaches the corresponding areas in the somatosensory cortices but, critically, also those multisensory areas mapping the left side of the external space. Thus, stimulation of each hand results in a mismatch between somatosensory and space-based representations (thin, green-red double arrow). Note that the neural connections between spatially corresponding areas of the somatotopic and space-based representations (eg, the somatotopic representation of the right hand and the representation of the right side of the external space) are stronger than those between areas of the somatotopic and space-based representations that do not correspond (see main text for an explanation of the reasons underlying this assumption). The mismatch between somatosensory and space-based representations results in a reduced perceived intensity of the delivered stimuli.

potentials), which better reflects the magnitude of the ascending somatosensory volley [27], was not affected by crossing the hands. This excludes the possibility that the change in body posture modulated the magnitude of the afferent somatosensory input. This finding is consistent with single-cell recordings in monkeys that showed that the neural responses in S1 are correlated to the intensity of the applied stimulus but not to its awareness [13]. In humans, a clear response of primary somatosensory neurons to tactile stimuli is observed even when the stimuli are below perceptual threshold [30]. In contrast, only late components of the somatosensory-evoked potentials are correlated with stimulus awareness [27,43,46,48]. Consistent with these observations, the observed reduction of perceived intensity consequent to crossing the arms was only reflected in the reduced magnitude of the late components of the response elicited by somatosensory stimuli (the N2-P2 wave of laser-evoked potentials), which, despite the difficulties related to the limited reliability of source analysis of EEG data and blind source separation approaches [39], have been suggested to be largely explained by neural activities arising from multimodal cortical areas [40]. Thus, the selective modulation of the N2-P2 response when the hands are crossed indicates that the observed analgesic effect is related to a modulation of the activity in multimodal cortical areas.

Which multimodal brain areas may be involved in this phenomenon? In both human and nonhuman primates, the posterior parietal cortex is important for the integration of spatial information coming from different sensory modalities [2,8,11,19,34]. In particular, the ventral aspect of the intraparietal sulcus, which divides the parietal lobe into the superior and the inferior parietal lobules [14], contains neurons that encode the information contained in stimuli belonging to different sensory modalities into a reference frame that can be accessed by all sensory systems [3]. Part of the human intraparietal sulcus has been shown to play a pivotal role in the multisensory representation of limb position [5,31]. Thus, this human area homologous to the ventral aspect of the intraparietal sulcus in nonhuman primates is also likely to be related to the modulation of both somatosensory perception (Fig. 1) and the magnitude of multimodal ERP components (Fig. 2).

This is the first evidence that disrupting the processes by which the brain localises a noxious stimulus reduces the pain evoked by that stimulus. The magnitude of the effect shown here is too small to be clinically important, but it reveals for the first time that the mechanisms by which a sensory event emerges into awareness can modulate pain. This extends a previous result that perceptual illusions can modulate pain [37], and raises a new possible explanation for the purported analgesic effect of mirror therapy, although that mirror analgesia is due to seeing the reflected image is not established, and other explanations are possible [36]. Finally, the current results lay the platform for future studies that maximise conflict between neural representations of a noxious stimulus according to somatotopic and space-based frames of reference, possibly resulting in larger and clinically important analgesic effects. Perhaps, when we get hurt, we should not only “rub it better” but also cross our arms.

Conflict of interest statement

The authors declare no conflict of interest.

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