American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY
ELSEVIER

The Journal of Pain, Vol 14, No 9 (September), 2013: pp 957-965
Available online at www.jpain.org and www.sciencedirect.com

Crossing the Line of Pain: fMRI Correlates of Crossed-Hands Analgesia

Diana M. Torta,[*,†] Matteo Diano,[*,†] Tommasco Costa,[*,†] Alberto Gallace,[‡] Sergio Duca,[†] Giuliano C. Geminiani,[*,†] and Franco Cauda[*,†]

[*]Department of Psychology, University of Turin, Turin, Italy.
[†]CCS fMRI-Brain Connectivity and Complex Systems Unit, Koelliker Hospital, Turin, Italy.
[‡]Department of Psychology, University of Milan-Bicocca, Milan, Italy.

Abstract: Crossing the hands over the body midline reduces the perceived intensity of nociceptive stimuli applied to the hands by impairing the ability to localize somatosensory stimuli. The neural basis of this "crossed-hands analgesia" has not been investigated previously, although it has been proposed that the effect may be modulated by multimodal areas. We used functional magnetic resonance imaging to test the hypothesis that crossed-hands analgesia is mediated by higher-order multimodal areas rather than by specific somatosensory ones. Participants lay in the scanner while mechanical painful stimuli were applied to their hands held in either a crossed or uncrossed position. They reported significantly lower perceived intensity of pain when their hands were crossed. Although activations elicited by stimuli applied to the crossed hands revealed significantly greater blood oxygen level–dependent responses in the anterior cingulate cortex, the insula, and the medial frontal gyrus, the blood oxygen level–dependent responses in the superior parietal lobe were greater with the hands uncrossed. Our results provide evidence that crossed-hands analgesia is mediated by higher-order frontoparietal multimodal areas involved in sustaining and updating body and spatial representations.

***Perspective:** We found crossed-hands analgesia to be mediated by multimodal areas, such as the posterior parietal, cingulate, and insular cortices, implicated in space and body representation. Our findings highlight how the perceived intensity of painful stimuli is shaped by how we represent our body and the space surrounding it.*

***Key words:** Frames of reference, pain, crossed-hands, fMRI, analgesia.*

Our ability to correctly determine to which hand nociceptive and non-nociceptive somatosensory stimuli are applied is reduced when the hands are crossed over the midline (the crossed-hands deficit[51]). It has been suggested that somatosensory stimuli are automatically mapped onto 2 frames of reference, 1 somatotopic and 1 body-centered[15]: the first related to where the stimulus is located on the skin, the second to where the stimulus is located in the space surrounding the body. Thus, on the basis of somatotopic frames of reference, stimuli applied to the left hand are always mapped as "left," regardless of the position of the hand. In contrast, on the basis of body-centered frames of reference, stimuli applied to the left hand placed in the right space can also be classified as "right," thus leading to a spatial conflict with the somatotopic representation of the stimulus.

Gallace et al[18] demonstrated that as a result of this mismatch, non-nociceptive and nociceptive stimuli applied to the crossed hands are perceived as less intense and elicit smaller event-related potentials (ERPs). Intriguingly, the authors found that only later components of ERPs (the N2-P2 complex[59]) were reduced, whereas early ones (N1) remained unchanged. Given the suggestion that later components of ERPs reflect multimodal processing and awareness of a somatosensory stimulus,[16,17,27,43,52] whereas earlier ones reflect its sensory-specific elaboration,[43] the authors proposed that the crossed-hands analgesia effect was mediated

Received September 21, 2012; Revised January 25, 2013; Accepted March 21, 2013.
This research was funded by the "Fondazione Molo."
The authors report no conflict of interest.
Supplementary data accompanying this article are available online at www.jpain.org and www.sciencedirect.com.
Address reprint requests to Diana M. Torta, PhD, Department of Psychology, University of Turin and CCS fMRI-Brain Connectivity and Complex Systems Unit, Koelliker Hospital, Via Po 14, 10123 Turin, Italy. E-mail: diana.torta@unito.it
1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2013.03.009

by disruption of higher-order multimodal area activity.[18] However, the spatial resolution of ERPs is generally poor; thus, definitive evidence upholding this hypothesis needs to be provided.

We used functional magnetic resonance imaging (fMRI) to characterize the areas representing the neural correlates of crossed-hands analgesia. As the N2-P2 complex is thought to originate from the anterior cingulate cortex/parietal operculum,[19] whereas the N1 from primary somatosensory cortices,[60] we hypothesized that if crossed-hands analgesia is mediated by higher-order multimodal areas, we should observe a change in the blood oxygen level–dependent (BOLD) response in the cingulate and parietal regions. However, as the primary somatosensory cortex (S1) is involved in the perception of intensity of nociceptive stimuli[41] and contains a somatotopic map of the body,[25,42] it may represent another substrate of crossed-hands analgesia not observed in previous studies[18] because of the methodology used. Indeed, a lack of modulation of N1 in a previous study could have been driven by the high variability in the detection and measurement of this component.[24]

The possibility that the disruption of higher-order multimodal areas activity, devoted to the integration of information of the body and the surrounding space,[38] imparts analgesic effects is interesting also under a clinical standpoint. Indeed, recent views underline the tight relation that exists between spatial integration, body perception, and pain processing. For instance, it has been demonstrated that patients with chronic pain (complex regional pain syndrome [CRPS] and unilateral low-back pain) present altered spatial representation of somatosensory stimuli.[39,40] Moseley and colleagues[39] asked CRPS patients to judge the order in which pairs of tactile stimuli were delivered on either hand, while participants held their hands either crossed or uncrossed. In the canonic uncrossed condition, patients prioritized stimuli from the unaffected limb; however, in the crossed condition, participants prioritized stimuli from the affected limb that was placed in the unaffected portion of space. These results indicate that the tactile deficit is dependent on the space in which normally the affected part of the body resided, and not on the affected limb itself. In addition, the same authors have recently shown that spontaneous pain in CRPS patients is reduced when the hands are crossed over the midline.[37] These evidences point to a crucial interplay between peripersonal space and the perception of pain.

Methods

Participants

Seventeen healthy volunteers (8 women, mean age 28 ± 4.2) took part in the study. Participants were recruited among staff and students of the University of Turin and all gave their written informed consent. Volunteers were all right-handers according to the Edinburgh Assessment Scale,[44] with no history of neurologic or psychiatric deficits. Professional musicians and skilled musicians were a priori excluded from this study as it has been shown that they may have competences that alleviate the crossed-hands deficit.[26] The study was carried out according to the standards required by the Declaration of Helsinki and was approved by the local ethics committee.

Experimental Procedure

Before entering the fMRI scanner, participants were instructed on the task and familiarized with the stimuli. During the experimental session they lay in the MRI scanner with their eyes closed. The stimuli were applied to the dorsum of their left and right hands while they held their arms either crossed or uncrossed over the body midline. In half of the trials the left arm was above the right one, and in the other half the position was inverted. Participants were made comfortable by placing a small mat under their arms. If necessary, 2 additional pieces of foam were placed under their elbows. The distance between hands (approximately 30 cm) was the same in both conditions. Each of the 4 blocks was composed of a pseudorandom sequence of 24 stimuli, 12 of which were delivered with the hands crossed and 12 with the hands uncrossed. Half of the participants began the experiment with their hands crossed, and the other half with their hands uncrossed. The interstimulus interval ranged pseudorandomly from 18 to 22 seconds. The experimenter (D.M.T.) changed the position of the hands in the middle of the block. No more than 3 stimuli were delivered consecutively to the same hand. Participants were required to relax, pay attention to all the stimuli, and provide a rating of their average intensity when the experimenter changed the position of the hands. The experimental procedure is shown in Fig 1.

Stimuli were applied using a hand-held 256-mN pinprick probe with a flat cylindrical tip (diameter: 250 μm). This device evokes a pinprick sensation primarily

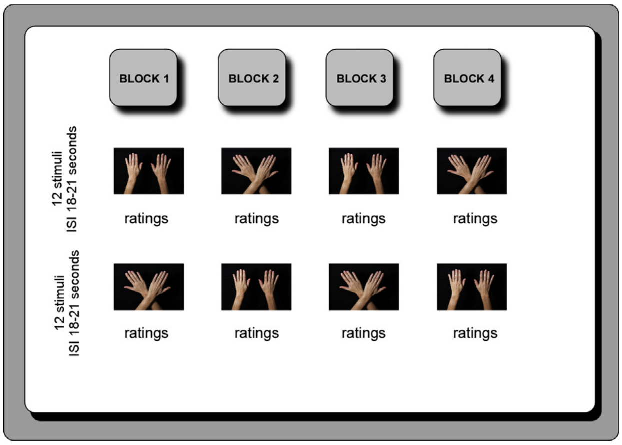

Figure 1. A schematic representation of the experimental procedure is shown here. Participants underwent 4 scans of a slow event-related paradigm in which mechanical painful stimuli were applied to their crossed or uncrossed hands. Half of the participants began the task with their hands uncrossed (sequence 1 to 4), the other half with their hands crossed (sequence 4 to 1). Participants rated the intensity of the stimuli in the middle and at the end of each block.

mediated by activation of type I A-delta mechano-heat receptors.[32,54] These stimulators represent an adequate tool for the induction of pinprick pain in psychophysical and clinical investigations[5,6,20,21,64] and are commonly used for quantitative sensory testing of neuropathic pain.[50] To avoid nociceptor fatigue, the stimulator was moved slightly after each stimulus.

Perceived Intensity

In order to investigate whether crossing the hands results in a significant reduction in the perceived intensity of mechanical painful stimuli, we asked each participant to rate the average intensity of the stimuli applied to the crossed and uncrossed hands on a numerical rating scale ranging from 0 (no pinprick sensation) to 10 (the strongest pinprick sensation imaginable). We obtained 2 ratings for each block, 1 in the middle of the block, when the position of the hands was changed, and the other at the end of the block. These ratings corresponded to the average perception of intensity elicited by stimuli delivered until that moment. For each participant, we collected 8 ratings (4 for each position, see Fig 1); these were averaged together to obtain a mean rating of the perceived intensity of pain elicited by pinprick stimuli in the crossed and uncrossed positions. We used a paired t-test to compare the average ratings for the crossed and uncrossed positions. In addition, we ran a 2-way repeated measures analysis of variance using as factors the "position" (2 levels, uncrossed vs crossed) and the "session" (4 levels, blocks 1, 2, 3, and 4). This latter analysis allowed us to examine the impact of the hands' position and order effects, and the interaction between them.

fMRI Procedure

Data acquisition was performed on a 1.5-T INTERA scanner (Philips Medical Systems, Eindhoven, The Netherlands) with a SENSE high-field, high-resolution (MRIDC) head coil optimized for functional imaging. Functional T2-weighted images were acquired using echoplanar sequences, with a repetition time of 2,000 ms, an echo time of 50 ms, and a 90° flip angle. The acquisition matrix was 64 × 64, with a 200-mm field of view. A total of 240 volumes were acquired, with each volume consisting of 19 axial slices, parallel to the anterior-posterior commissure; slice thickness was 4.5 mm with a .5-mm gap.

Within a single session, for each participant, before the BOLD acquisition, a set of 3-dimensional (3D) high-resolution T1-weighted structural images was acquired, using a fast field echo sequence, with a 25-ms repetition time, an ultrashort echo time, and a 30° flip angle. The acquisition matrix was 256 × 256, and the field of view was 256 mm. The set consisted of 160 contiguous sagittal images covering the whole brain. In-plane resolution was 1 mm × 1 mm and slice thickness was 1 mm.

BOLD imaging data were preprocessed and analyzed using the BrainVoyager QX software (Brain Innovation, Maastricht, The Netherlands). The first 2 scans were directly removed by the scanner for signal equilibration. Functional images were preprocessed by computing, for each slice, the average intensity across the first image; for each subsequent scan of the same slice, we computed the mean intensity and then scaled it to result in the same average slice intensity. We performed 3D motion correction to correct small head movements by spatially aligning all volumes to the first volume by rigid body transformations, using a trilinear interpolation algorithm. We performed a slice scan time correction to allow a whole volume to be treated as a single data point: the sequentially scanned slices comprising each volume were interpolated in time, using a signal sinc-interpolation algorithm. We also performed spatial data smoothing using a 3D Gaussian kernel with a full width at half maximum (FWHM) of 8 mm. We used temporal filters to remove drifts due to scanner and physiological noise: we performed linear and nonlinear trend removal through a temporal high-pass filter eliminating frequencies lower than 3 cycles in time course (.0012 Hz) and we set a low-pass filter to 2.8-second Gaussian FWHM. Subsequently, we followed a series of steps to allow for precise anatomic location of brain activity to facilitate intersubject averaging. Each subject's slice-based functional scan was coregistered with their 3D high-resolution structural scan. Next, the 3D structural data set of each subject was transformed into Talairach space[57]: The cerebrum was translated and rotated into the anterior-posterior commissure plane and then the borders of the cerebrum were identified. Finally, using the anatomo-functional coregistration matrix and the determined Talairach reference points, the functional time course of each subject was transformed into Talairach space and the volume time course created.

In order to compute the voxel-wise group analyses, we specified a multisubject design matrix and convolved each defined box-car with a predefined hemodynamic response function to account for the hemodynamic delay.[8] A statistical group analysis using the general linear model with separate subject predictors was performed on the group to yield random-effect functional activation maps. To ensure that the stimuli elicited activations in the pain-related network, we first performed a contrast versus the baseline (crossed vs baseline [ie, rest] and uncrossed vs baseline). Subsequently, we contrasted cerebral activations elicited by stimuli applied to the crossed hands and those elicited by stimuli applied to the uncrossed hands (crossed vs uncrossed) to disclose the effects of crossing the hands on cerebral activations and deactivations. Such contrasts were obtained by using all stimuli delivered to the hands when they were crossed and uncrossed regardless the side of stimulation (left or right).

All statistical comparisons were made on z-transformed time courses and were computed at a statistical threshold of $P < .05$ corrected for multiple comparisons using false discovery rate correction.[7]

As the act of crossing the hands per se might have affected brain activity, we created 2 different baselines, accounting for the effect of "position." For the analysis of the crossed condition, we employed the baseline acquired during rest periods in which participants

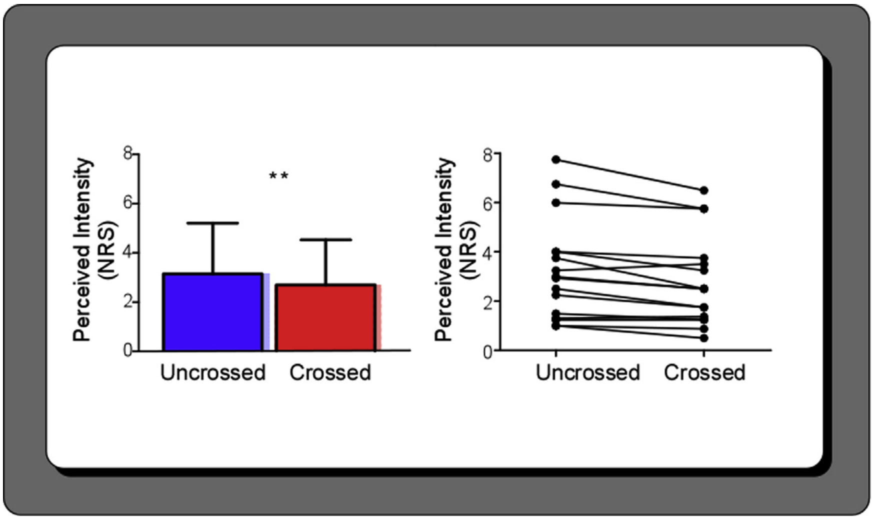

Figure 2. Behavioral findings. Participants perceived stimuli as significantly less intense when their hands were crossed ($P < .0001$). This effect was small but consistent across participants (right panel). **$P < .001$.

held their hands crossed, and for analysis of the uncrossed condition, we employed the baseline acquired during rest periods with the hands in the uncrossed position.

We performed a region of interest (ROI) analysis on S1 to test any possible involvement of this area in crossed-hands analgesia. We created the ROI by using a functional localizer derived from the same data set, using an orthogonal contrast (uncrossed AND crossed) to avoid circularity. A random-effect generalized linear model was then applied to the time course of each ROI, comparing uncrossed activations with crossed activations ([crossed—baseline crossed] − [uncrossed—baseline uncrossed]).

Results

Behavioral Results: Perceived Intensity

The average ratings of intensity elicited by pinprick stimulation were 3.1 (±2) when the hands were uncrossed and 2.7 (±1.8) when the hands were crossed. A t-test comparison revealed that the difference was significant, $t(16) = 4.098$, $P = .001$. This indicates that the perceived intensity of the stimuli was reduced when the hands were crossed. The repeated measures analysis of variance highlighted a significant main effect of "position," $F(1, 6) = 16.795$, $P < .001$, but no significant main effect of "session," $F(3, 48) = 1.354$, $P = .268$. Interaction

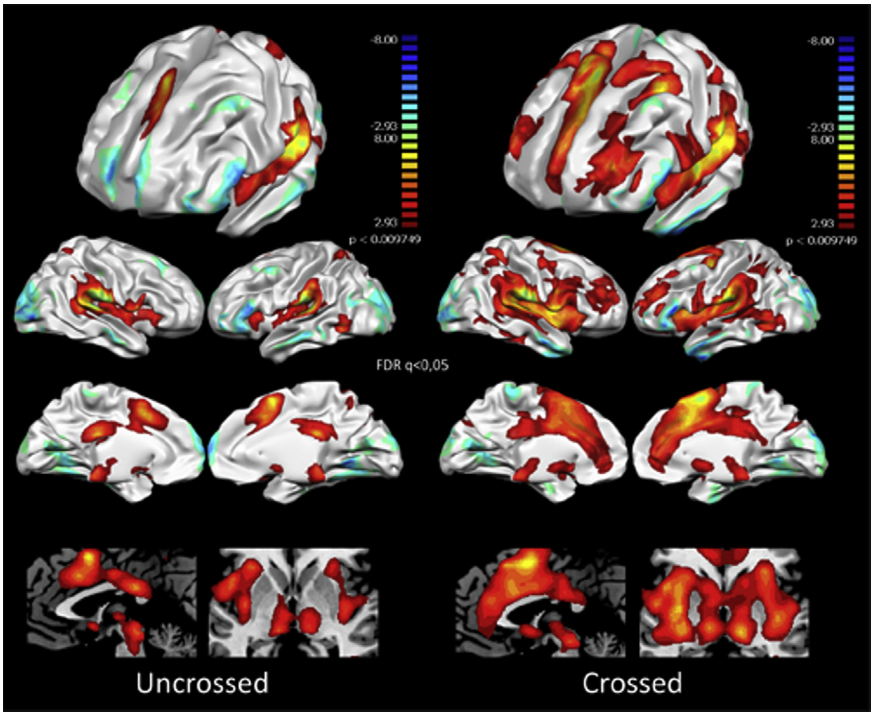

Figure 3. Brain activity generated by stimuli contrasted with the baseline (rest). Notably, mechanical painful stimuli generated activation across a range of cortical areas including the insular, cingulate, frontal, and somatosensory cortices.

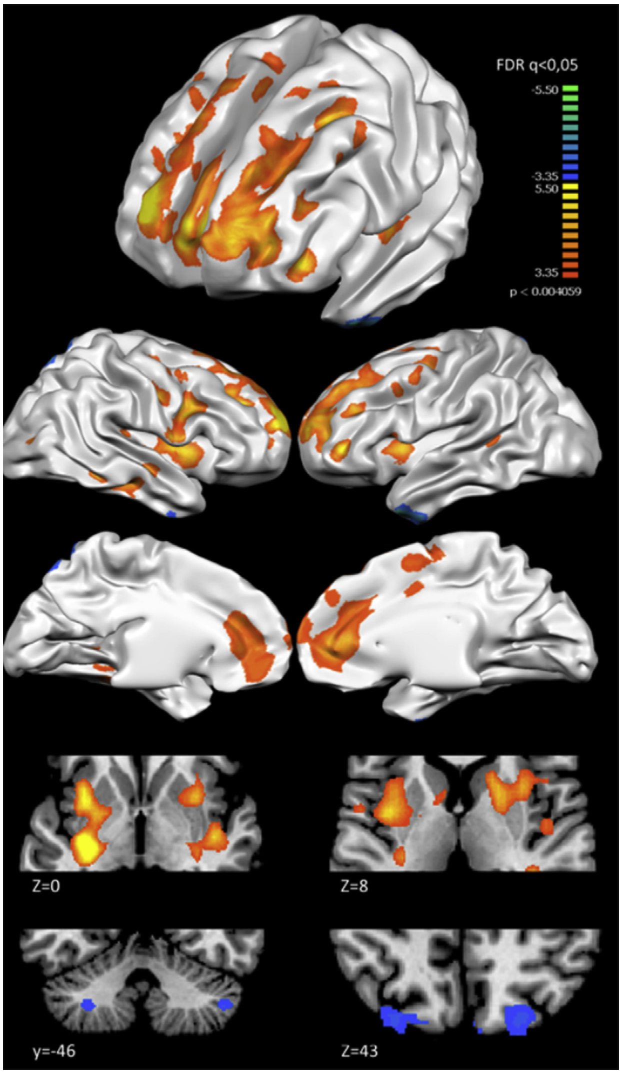

Figure 4. The comparison between the crossed and uncrossed conditions revealed that stimuli applied to the crossed hands elicited greater BOLD responses in the cingulate, insular, and frontal regions. In contrast, stimuli applied to the uncrossed hands elicited greater BOLD responses in the superior parietal lobe, in line with the proposal that crossed-hands analgesia stems from a mismatch between spatial frames of reference.

effects were also not significant, F(3, 48) = 2.002, $P = .126$. This indicates that the crossed-hands analgesia lasted for the whole experimental session.

As it can be seen in Fig 2, this effect was consistently observed across participants, suggesting that crossed-hands analgesia was a small but recurrent effect that occurred whenever the participants crossed their hands over the body midline (see also[18]).

fMRI Results: General Linear Model

All figures show significant results with a threshold of $P < .05$ and corrected for multiple comparisons (ie, false discovery rate correction). Activations elicited by stimuli applied to the crossed (crossed vs baseline) and uncrossed (uncrossed vs baseline) hands were found in the primary and secondary somatosensory cortices, in the cingulate and frontal cortices, in the insula, and in the thalamus, thus confirming that stimuli activated the network of areas devoted to the elaboration of nociceptive stimuli[2,14,47,58] (see Fig 3).

The analysis of the contrast between the crossed and uncrossed positions revealed that stimuli applied to the crossed hands elicited significantly greater BOLD responses in the anterior cingulate cortex, the insula, and in the medial frontal gyrus. In contrast, BOLD responses in the superior parietal lobe and in the brainstem were greater when the hands were uncrossed (see Fig 4 and Supplementary Fig 1). A summary of the significant results can be found in Table 1.

The ROI analysis on S1 did not reveal any significant difference between conditions, thus confirming that S1 is not involved in crossed-hands analgesia.

Discussion

It has been proposed that the analgesic effect imparted by crossing the hands over the body midline involves the activity of multimodal but not specific somatosensory areas.[18] In order to investigate this hypothesis, we applied mechanical painful stimuli when participants held their hands in a crossed or uncrossed position while undergoing fMRI. We observed 2 main findings. First, crossing the hands over the body midline reduces the subjective perception of intensity of mechanical painful stimuli, as it reduces that of laser and electrical stimuli.[18] Second, stimuli applied to the crossed hands elicit greater activation of the anterior cingulate, insular, and prefrontal cortices as compared to stimuli applied to the uncrossed hands, which, in contrast, elicit greater activity in the superior parietal lobe.

Crossed-Hands Analgesia for Mechanical Stimuli

In a previous study, Gallace and colleagues[18] reported that the perception of both nociceptive (laser) and non-nociceptive (electrical) stimuli is reduced when the hands are crossed over the midline. We have demonstrated that crossed-hands analgesia also applies to mechanical painful stimuli. It has been proposed that this effect is a consequence of the mismatch between somatotopic and body-centered frames of reference onto which somatosensory stimuli are mapped.[18] This explanation is supported by a recent study in which the authors asked participants to perform a temporal order judgment task wherein pairs of tactile or nociceptive stimuli were applied to the uncrossed or crossed hands in rapid succession. The authors observed a significant impairment in the identification of which hand was stimulated first (or second) when the hands were crossed.[51] This deficit clearly indicates that nociceptive stimuli cannot be localized solely on the basis of somatotopic references, relying on a somatotopic representation of the hand in S1.[51] Indeed, if nociceptive stimuli were localized exclusively on the basis of somatotopic frames of reference, the position of the hand would not affect performance as stimuli applied to the right hand are always mapped on the same somatotopic references of the right hand

Table 1. Brain Regions Showing a Significant Increase (Crossed > Uncrossed) or Decrease (Crossed < Uncrossed) in BOLD Signal

Areas	BA	x	y	z	t	P
Crossed > Uncrossed						
Right insula	13	36	3	6	3.44	<.005
Left insula	13	−37	13	12	3.97	<.004
Left anterior cingulate cortex	32	−12	42	0	4.39	<.0001
Right anterior cingulate cortex	24	7	36	8	4.14	<.0001
Right medial frontal gyrus	10	10	56	17	2.62	<.01
Right superior frontal gyrus	9/10	15	55	21	6.85	<.0001
Left superior frontal gyrus	9/10	−13	42	16	3.87	<.001
Left medial temporal gyrus	9	−10	36	19	4.031	<.0009
Right superior temporal gyrus	22	38	−22	−1	4.95	<.001
Uncrossed > Crossed						
Right superior parietal lobe	7	15	−67	56	−3.75	<.0001
Left superior parietal lobe	7	−4	−63	56	−4.83	<.0001
Left middle temporal gyrus	21	−46	8	−31	−4.17	<.0001
Right middle temporal gyrus	21	37	−2	−31	−3.70	<.001
Left brainstem		−5	−27	−35	−3.63	<.002
Right cerebellum		30	−43	38	−3.53	<.001
Right inferior frontal gyrus	9	−40	7	29	−4.50	<.003

Abbreviation: BA, brodmann area.
NOTE. Coordinates are provided in Talairach space.

regardless of where the right hand is placed in the peripersonal space.

Neural Substrates of Crossed-Hands Analgesia

The dissociation between later and earlier components of the laser and somatosensory-evoked potentials observed by Gallace and colleagues[18] led the authors to propose that crossed-hands analgesia is mediated by higher-order multimodal areas. However, using ERPs, detailed anatomic localization was not possible. Our findings substantiate that suggestion. Specifically, we observed that the anterior cingulate, frontal, and anterior insular cortices were more active when the hands were crossed. In contrast, and interestingly, greater activations were observed in the posterior parietal cortex when the hands were uncrossed.

Besides being areas of the so-called pain neuromatrix,[2,12,47] the anterior cingulate, insular, and frontal cortices have been proposed to be part of the "body matrix," a network of areas devoted to the integration of spatial and somatotopic information with the purpose of supporting a coherent representation of the body and protecting its integrity at both a physiological (ie, homeostatic) and psychological (ie, body awareness) level.[38] Thus, increased activation of such frontal multimodal regions in the crossed-hands condition may reflect the greater cognitive load required to locate the stimulus and may also be related to the necessity to update the body schema containing information on the position of the body in space (see[23]). In line with the latter suggestion is evidence that the superior and medial frontal gyri, more active in the crossed condition, are part of a brain network devoted to internal processing.[22,35,53] In either case, the need for such additional cognitive activity is likely to have limited the neural resources available to elaborate the stimulus, thus imparting an analgesic effect. Increased activation of frontal areas, negatively correlated with the perceived intensity of the painful stimulus,[4,31,48] has been observed when subjects are distracted from a painful stimulus or are required to perform a cognitive task during the application of a painful stimulus.[13,61]

Crucially, our results also point to a reduced activation of the superior parietal lobe in the crossed condition. This finding highlights the implication of a spatial mechanism in the analgesic effect of crossing the hands. Activation of the superior parietal lobe, which is considered the human homolog of the intraparietal sulcus in monkeys,[10] has been linked to the representation of the peripersonal space and the multisensory integration of visual and proprioceptive inputs,[3,33,46] whereas lesions in this region and its connections frequently produce spatial disorders such as neglect.[9,11,36,62,63] Although brain-damaged patients fail to report somatosensory stimuli delivered to the hand placed in the neglected portion of space (most likely the left hand after a lesion in the right hemisphere), they detect more touches when their hands are crossed over the body midline.[1,55] This finding underlines the existence of a flexible interplay between the representation of space and the perception of somatosensory stimuli. Moreover, transcranial magnetic stimulation studies indicate that when activity in the posterior parietal cortex is inhibited, the ability to localize both nociceptive and non-nociceptive somatosensory stimuli is greatly impaired.[49] On the same line, fMRI studies have demonstrated a crucial role of the posterior parietal lobe in the process of localizing nociceptive stimuli applied to the body.[45]

Taken as a whole, these findings uphold the interpretation of crossed-hands analgesia as being mediated by multimodal brain areas as a result of the failure to localize the stimuli.

These findings have also important clinical implications. Indeed, a growing body of evidence is showing that analgesic effects can be obtained by looking at the parts of the body to which stimuli are applied[29,30,34] or by using prismatic lenses that shift the focus of attention away from the part of body in pain.[56] Second, our results highlight the importance of the interplay among spatial and body representations in the perception of nociceptive stimuli. For instance, Liu et al[28] demonstrated that neglect patients fail to report nociceptive stimuli applied to the hand contralateral to the lesion when a concomitant nociceptive stimulus is applied to the hand ipsilateral to the lesion (neglect extinction). In addition, Moseley and colleagues[39] found that patients having CRPS tend to prioritize stimuli delivered to the unaffected hand when the hands are uncrossed, but to prioritize those delivered to the *affected* hand when this is located in the space normally occupied by the unaffected one.

Thus, converging evidence highlights that there is a tight connection between how threatening, painful stimuli are localized in the peripersonal space and how they are perceived.

One limitation of this study is that we did not use tactile stimuli as a control. However, as previous evidence suggests that the perception of both nociceptive and non-nociceptive stimuli is modulated by crossing the hands,[18,51] our prediction is that very similar findings might be obtained by using tactile stimuli. In addition, the clinical importance of the crossed-hands analgesia still needs to be validated in experimentally induced pain in patients having chronic pain. Related to this possibility, Moseley and colleagues[37] have shown that crossing the hands over the midline for 10 minutes reduces spontaneous pain from the affected hand in CRPS patients. Finally, as for what concerns possible methodologic limitations, it can be that the poor temporal resolution caused by the low sample rate of fMRI together with the physiological hemodynamic delay did not allow us to disentangle response differences that occurred at very fast temporal windows. In this sense some aspects of the crossed-hands effect might have been underdetected.

In conclusion, our findings indicate that the analgesic effect of crossing the hands involves the activity of higher-order multimodal brain areas. Importantly, this analgesic effect does not exclusively depend on a reduction of cognitive resources, but stems from the conflict between different spatial frames of reference used to localize painful stimuli.

Acknowledgments

The authors would like to thank Drs Giandomenico Iannetti, Martina Amanzio, and Walter Magerl for their help and suggestions.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpain.2013.03.009.

References

1. Aglioti S, Smania N, Peru A: Frames of reference for mapping tactile stimuli in brain-damaged patients. J Cogn Neurosci 11:67-79, 1999

2. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK: Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 9:463-484, 2005

3. Avillac M, Deneve S, Olivier E, Pouget A, Duhamel JR: Reference frames for representing visual and tactile locations in parietal cortex. Nat Neurosci 8:941-949, 2005

4. Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I: Imaging how attention modulates pain in humans using functional MRI. Brain 125:310-319, 2002

5. Baumgartner U, Iannetti GD, Zambreanu L, Stoeter P, Treede RD, Tracey I: Multiple somatotopic representations of heat and mechanical pain in the operculo-insular cortex: A high-resolution fMRI study. J Neurophysiol 104:2863-2872, 2010

6. Baumgartner U, Magerl W, Klein T, Hopf HC, Treede RD: Neurogenic hyperalgesia versus painful hypoalgesia: Two distinct mechanisms of neuropathic pain. Pain 96:141-151, 2002

7. Benjamini Y, Hochberg Y: Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc Ser B 57:289-300, 1995

8. Boynton GM, Engel SA, Glover GH, Heeger DJ: Linear systems analysis of functional magnetic resonance imaging in human V1. J Neurosci 16:4207-4221, 1996

9. Committeri G, Pitzalis S, Galati G, Patria F, Pelle G, Sabatini U, Castriota-Scanderbeg A, Piccardi L, Guariglia C, Pizzamiglio L: Neural bases of personal and extrapersonal neglect in humans. Brain 130:431-441, 2007

10. Culham JC, Kanwisher NG: Neuroimaging of cognitive functions in human parietal cortex. Curr Opin Neurobiol 11:157-163, 2001

11. Doricchi F, Thiebaut de Schotten M, Tomaiuolo F, Bartolomeo P: White matter (dis)connections and gray matter (dys)functions in visual neglect: Gaining insights into the brain networks of spatial awareness. Cortex 44: 983-995, 2008

12. Duerden EG, Albanese MC: Localization of pain-related brain activation: A meta-analysis of neuroimaging data. Hum Brain Mapp 34:109-149, 2011

13. Frankenstein UN, Richter W, McIntyre MC, Remy F: Distraction modulates anterior cingulate gyrus activations during the cold pressor test. Neuroimage 14:827-836, 2001

14. Friebel U, Eickhoff SB, Lotze M: Coordinate-based meta-analysis of experimentally induced and chronic persistent neuropathic pain. Neuroimage 58:1070-1080, 2011

15. Gallace A, Soto-Faraco S, Dalton P, Kreukniet B, Spence C: Response requirements modulate tactile spatial congruency effects. Exp Brain Res 191:171-186, 2008

16. Gallace A, Spence C: The cognitive and neural correlates of "tactile consciousness": A multisensory perspective. Conscious Cogn 17:370-407, 2008

17. Gallace A, Spence C: The role of somatosensory cortex in the awareness of tactile information. Psyche (Stuttg) 16: 30-67, 2010

18. Gallace A, Torta DM, Moseley GL, Iannetti GD: The analgesic effect of crossing the arms. Pain 152:1418-1423, 2011

19. Garcia-Larrea L, Frot M, Valeriani M: Brain generators of laser-evoked potentials: From dipoles to functional significance. Neurophysiol Clin 33:279-292, 2003

20. Greenspan JD, McGillis SL: Thresholds for the perception of pressure, sharpness, and mechanically evoked cutaneous pain: Effects of laterality and repeated testing. Somatosens Motor Res 11:311-317, 1994

21. Greenspan JD, Thomadaki M, McGillis SL: Spatial summation of perceived pressure, sharpness and mechanically evoked cutaneous pain. Somatosens Motor Res 14: 107-112, 1997

22. Greicius MD, Krasnow B, Reiss AL, Menon V: Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A 100: 253-258, 2003

23. Haggard P, Wolpert DM: Disorders of body scheme, in Freund H-J, Jeannerod M, Hallett M, Leiguarda R (eds): Higher-Order Motor Disorders: From Neuroanatomy and Neurobiology to Clinical Neurology. New York, NY, Oxford University Press, 2005, pp 261-271

24. Hu L, Mouraux A, Hu Y, Iannetti GD: A novel approach for enhancing the signal-to-noise ratio and detecting automatically event-related potentials (ERPs) in single trials. Neuroimage 50:99-111, 2010

25. Kaas JH: What, if anything, is SI? Organization of first somatosensory area of cortex. Physiol Rev 63:206-231, 1983

26. 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 400:163-167, 2006

27. Lee MC, Mouraux A, Iannetti GD: Characterizing the cortical activity through which pain emerges from nociception. J Neurosci 29:7909-7916, 2009

28. 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 152:498-506, 2011

29. Longo MR, Betti V, Aglioti SM, Haggard P: Visually induced analgesia: Seeing the body reduces pain. J Neurosci 29:12125-12130, 2009

30. Longo MR, Iannetti GD, Mancini F, Driver J, Haggard P: Linking pain and the body: Neural correlates of visually induced analgesia. J Neurosci 32:2601-2607, 2012

31. Lorenz J, Garcia-Larrea L: Contribution of attentional and cognitive factors to laser evoked brain potentials. Neurophysiol Clin 33:293-301, 2003

32. Magerl W, Fuchs PN, Meyer RA, Treede RD: Roles of capsaicin-insensitive nociceptors in cutaneous pain and secondary hyperalgesia. Brain 124:1754-1764, 2001

33. Makin TR, Holmes NP, Zohary E: Is that near my hand? Multisensory representation of peripersonal space in human intraparietal sulcus. J Neurosci 27:731-740, 2007

34. Mancini F, Longo MR, Kammers MP, Haggard P: Visual distortion of body size modulates pain perception. Psychol Sci 22:325-330, 2011

35. Mantini D, Perrucci MG, Del Gratta C, Romani GL, Corbetta M: Electrophysiological signatures of resting state networks in the human brain. Proc Natl Acad Sci U S A 104: 13170-13175, 2007

36. Mort DJ, Malhotra P, Mannan SK, Rorden C, Pambakian A, Kennard C, Husain M: The anatomy of visual neglect. Brain 126:1986-1997, 2003

37. Moseley GL, Gallace A, Iannetti GD: Spatially defined modulation of skin temperature and hand ownership of both hands in patients with unilateral complex regional pain syndrome. Brain 135:3676-3686, 2012

38. 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 36:34-46, 2012

39. 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 132:3142-3151, 2009

40. Moseley GL, Gallagher L, Gallace A: Neglect-like tactile dysfunction in chronic back pain. Neurology 79:327-332, 2012

41. Moulton EA, Pendse G, Becerra LR, Borsook D: BOLD responses in somatosensory cortices better reflect heat sensation than pain. J Neurosci 32:6024-6031, 2012

42. Mountcastle VB: The Sensory Hand: Neural Mechanisms of Somatic Sensation. Cambridge, MA, Harvard University Press, 2005

43. Mouraux A, Iannetti GD: Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. J Neurophysiol 101:3258-3269, 2009

44. Oldfield RC: The assessment and analysis of handedness: The Edinburgh Inventory. Neuropsychologia 9:97-113, 1971

45. Oshiro Y, Quevedo AS, McHaffie JG, Kraft RA, Coghill RC: Brain mechanisms supporting spatial discrimination of pain. J Neurosci 27:3388-3394, 2007

46. Pasalar S, Ro T, Beauchamp MS: TMS of posterior parietal cortex disrupts visual tactile multisensory integration. Eur J Neurosci 31:1783-1790, 2010

47. Peyron R, Laurent B, Garcia-Larrea L: Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol Clin 30:263-288, 2000

48. Porro CA, Cettolo V, Francescato MP, Baraldi P: Temporal and intensity coding of pain in human cortex. J Neurophysiol 80:3312-3320, 1998

49. Porro CA, Martinig M, Facchin P, Maieron M, Jones AK, Fadiga L: Parietal cortex involvement in the localization of tactile and noxious mechanical stimuli: A transcranial magnetic stimulation study. Behav Brain Res 178:183-189, 2007

50. Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, Treede RD: Quantitative sensory testing: A comprehensive protocol for clinical trials. Eur J Pain 10: 77-88, 2006

51. Sambo CF, Torta DM, Gallace A, Liang M, Moseley GL, Iannetti GD: The temporal order judgement of tactile and nociceptive stimuli is impaired by crossing the hands over the body midline. Pain 154:242-247, 2013

52. Schubert R, Blankenburg F, Lemm S, Villringer A, Curio G: Now you feel it–now you don't: ERP correlates

of somatosensory awareness. Psychophysiology 43:31-40, 2006

53. Shulman GL, Corbetta M, Buckner RL, Raichle ME, Fiez JA, Miezin FM, Petersen SE: Top-down modulation of early sensory cortex. Cereb Cortex 7:193-206, 1997

54. Slugg RM, Meyer RA, Campbell JN: Response of cutaneous A- and C-fiber nociceptors in the monkey to controlled-force stimuli. J Neurophysiol 83:2179-2191, 2000

55. Smania N, Aglioti S: Sensory and spatial components of somaesthetic deficits following right brain damage. Neurology 45:1725-1730, 1995

56. Sumitani M, Rossetti Y, Shibata M, Matsuda Y, Sakaue G, Inoue T, Mashimo T, Miyauchi S: Prism adaptation to optical deviation alleviates pathologic pain. Neurology 68:128-133, 2007

57. Talairach J, Tournoux P: Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Cerebral Imaging. New York, NY, Thieme, 1988

58. Treede RD, Kenshalo DR, Gracely RH, Jones AK: The cortical representation of pain. Pain 79:105-111, 1999

59. Treede RD, Kief S, Holzer T, Bromm B: Late somatosensory evoked cerebral potentials in response to cutaneous heat stimuli. Electroencephalogr Clin Neurophysiol 70: 429-441, 1988

60. Valentini E, Hu L, Chakrabarti B, Aglioti SM, Hu Y, Iannetti GD: The primary somatosensory cortex largely contributes to the early part of the cortical response elicited by nociceptive stimuli. Neuroimage 59:1571-1581, 2012

61. Valet M, Sprenger T, Boecker H, Willoch F, Rummeny E, Conrad B, Erhard P, Tolle TR: Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain—An fMRI analysis. Pain 109:399-408, 2004

62. Vallar G: Extrapersonal visual unilateral spatial neglect and its neuroanatomy. Neuroimage 14:S52-S58, 2001

63. Vallar G, Perani D: The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man. Neuropsychologia 24:609-622, 1986

64. Ziegler EA, Magerl W, Meyer RA, Treede RD: Secondary hyperalgesia to punctate mechanical stimuli. Central sensitization to A-fibre nociceptor input. Brain 122(Pt 12): 2245-2257, 1999