Title
A dual-brain approach for understanding the neuralmechanisms that underlie the comforting effects of social touch

Authors
Korisky, Adi
Eisenberger, Naomi I
Nevat, Michael
et al.

Publication Date
2020-06-01

DOI
10.1016/j.cortex.2020.01.028

Peer reviewed

CORTEX 127 (2020) 333–346

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Special Issue "Understanding Others": Research Report

A dual-brain approach for understanding the neuralmechanisms that underlie the comforting effects of social touch

Adi Korisky [a,d], *Naomi I. Eisenberger* [b], *Michael Nevat* [a], *Irit Weissman-Fogel* [c] *and Simone G. Shamay-Tsoory* [a,*]

[a] *Department of Psychology, University of Haifa, Haifa, Israel*
[b] *Department of Psychology, University of California, Los Angeles, CA, USA*
[c] *Department of Physical Therapy, University of Haifa, Haifa, Israel*
[d] *The Leslie and Susan Gonda Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat Gan, Israel*

ARTICLE INFO

Article history:
Received 15 May 2019
Reviewed 8 October 2019
Revised 8 December 2019
Accepted 27 January 2020
Published online 11 March 2020

Keywords:
Social touch
Pain
Hand-holding
Inferior parietal lobule
Emotion regulation

ABSTRACT

Across different cultures, social touch is used to alleviate distress. Here we adopt a dual-brain approach with fMRI to examine whether social touch involves similar activations between the suffering 'target' and the empathizer in brain regions related to emotional sharing such as the observation-execution (mirror) network. To inspect the neural underpinnings of the effects of social touch on pain, we scanned romantic couples during a task that required one partner (the empathizer) to hold the target's hand as the latter experienced painful thermal stimulation. Empathizers and target participants were scanned sequentially, in two counterbalanced phases. Results revealed that hand-holding reduced the pain of the target participant, compared to the severity of pain in a control condition (holding a rubber ball). Importantly, during social touch we found striking shared activations between the target and empathizer in the inferior parietal lobule (IPL), a region related to the observation-execution network. The brain-to-brain analysis further revealed a positive correlation of IPL activation levels between the target and the empathizer. Finally, psychophysiological interaction (PPI) analysis in the target showed that the IPL activity during social touch was positively coupled with activity in the dorsomedial prefrontal cortex, a region that has been implicated in emotion regulation, suggesting that the interaction between the observation-execution network and emotion regulation network may contribute to pain reduction during social touch.

Abbreviations: IPL, inferior parietal lobule; IFG, inferior frontal gyrus; ACC, anterior cingulate cortex; AI, anterior insula; OE, observation-execution; dmPFC, dorsomedial prefrontal cortex; fMRI, functional magnetic resonance imaging; PPI, psychophysiological interaction.

* *Corresponding author*. Department of Psychology, University of Haifa, Haifa, Israel.
E-mail address: sshamay@psy.haifa.ac.il (S.G. Shamay-Tsoory).

https://doi.org/10.1016/j.cortex.2020.01.028

1. Introduction

In humans, across radically different cultures, social touch is observed in kin and non-kin alike and involves similar behaviors, including soothing touch, hand-holding and skin-to-skin contact (Dibiase & Gunnoe, 2004; Jones & Yarbrough, 1985; Suvilehto, Glerean, Dunbar, Hari, & Nummenmaa, 2015). It has been shown that social touch elevates romantic satisfaction (Gallace & Spence, 2010) and reduces negative feelings (Coan, Schaefer, & Davidson, 2006; Ditzen et al., 2007; Grewen, Anderson, Girdler, & Light, 2003). Jakubiak et al. (2016) demonstrated that merely imagining social touch from a significant other reduces the subjective level of pain even more than verbal support. Specifically, it has been shown that hand-holding can diminish emotional distress as well as physical pain (Coan et al., 2006; Goldstein, Weissman-Fogel, Dumas, & Shamay-Tsoory, 2018; Kawamichi, Kitada, Yoshihara, Takahashi, & Sadato, 2015; Master et al., 2009; von Mohr, Krahé, Beck, & Fotopoulou, 2018).

Given that touch has been repeatedly found to reduce distress, an increasing amount of research has explored the neural underpinnings of social touch in humans. In general, these studies have followed one of two different directions. The first direction focused on the 'target' of pain, exploring why social touch reduces pain and distress. These studies have shown that while nociceptive stimuli commonly elicit activity in a wide array of subcortical and cortical brain structures that includes the somatosensory cortices, the thalamus, anterior cingulate cortex (ACC) and the insula (Apkarian, Bushnell, Treede, & Zubieta, 2005; Garcia-Larrea, Frot, & Valeriani, 2003; Treede, Kenshalo, Gracely, & Jones, 1999), social touch attenuates activation in these regions (Coan et al., 2006). In addition, electrophysiological studies show that touch can modulate pain in early (N1) and late (N2–P2) processing stages (Krahé, Drabek, Paloyelis, & Fotopoulou, 2016; von Mohr et al., 2018).

The second line of research has examined the behavioral and neural underpinnings of the empathizer's behavior. These studies have shown that social touch is an other-directed prosocial behavior driven by empathy, the ability to understand and/or feel other people's emotions (Batson, 2009; Peled-Avron, Goldstein, Yellinek, Weissman-Fogel, & Shamay-Tsoory, 2018; [1]de Waal & Aureli, 1996). Indeed, neuroimaging studies have shown that comforting others in distress activates empathy related regions, such as the medial prefrontal cortex, the insula and the ACC (Goldstein et al., 2018; Masten, Morelli, & Eisenberger, 2011; Mathur, Harada, Lipke, & Chiao, 2010) as well as reward related regions such as the ventral and dorsal striatum (Harbaugh, Mayr, & Burghart, 2007; Telzer, Masten, Berkman, Lieberman, & Fuligni, 2010, 2011). It was also reported that holding the hand of a partner in distress can modulate one's reward and maternal-behaviors related neural regions (Inagaki & Eisenberger, 2012).

However, which neural systems underlie the effect of touch on pain remains unknown because traditional imaging single brain approaches are unable to assess both sides of the interaction. Indeed, a new approach in neuroscience holds that social interactions by their nature entail active participation in an interactive social exchange with social agents (Schilbach et al., 2013; Shamay-Tsoory & Mendelsohn, 2019). Therefore, understanding the mechanism underlying the comforting effect of social touch requires developing a methodology that allows drawing direct links between brain activity of the empathizer and the target during real-life interactions. Previous human imaging studies focusing on empathy for another's pain have shown activations in regions involved in the direct experience of pain (Decety & Lamm, 2006; Jackson & Decety, 2004; Singer et al., 2004). In their comprehensive meta-analysis, Lamm, Decety, and Singer (2011) showed that during empathy for pain, there is consistent activation in both the dorsal ACC and anterior insula (AI), regions often associated with the affective or unpleasant component of physical pain (Tölle et al., 1999), as well as the inferior frontal gyrus (IFG) and inferior parietal lobule (IPL) which relate to observation-execution (OE) processes – the ability to observe specific actions and execute those actions in the same manner (also known as the mirror neuron system, see Rizzolatti & Craighero, 2004). This overlap between regions activated during vicarious pain and self-experienced pain implies that in addition to shared brain responses of pain, empathy for pain may involve mechanisms that underlie observation-execution. The OE system may be activated in both the empathizer and the target, suggesting that shared activations in the OE system between the empathizer and the target may contribute to the effectiveness of social touch. This hypothesis is in line with a recent EEG hyperscanning study, reporting that brain-to-brain coupling in the alpha/mu band in romantic couples during hand-holding predicts analgesia magnitude (Goldstein et al., 2018).

The current study was a functional imaging study aimed at examining the neural underpinnings of the comforting effect of social touch, by directly probing the neural correlates of social touch in the empathizer and the target. This allowed us to examine the effect of touch using paradigm with high ecological validity. Romantic couples were scanned during a social touch paradigm in which one of them ('the target') received high or low heat stimulation ('pain' and 'no pain' conditions, respectively), while the other partner ('the empathizer') held their hand ('human touch') or both partners held a rubber ball ('non-human touch'). We selected hand-holding as the type of touch based on recent studies showing that this type of touch is very common across different types of social bonds (Suvilehto et al., 2015) and it is one of the preferable types of touch for pain reduction (Goldstein et al., 2018). Two counterbalanced scans were conducted one after the other in order to allow scanning of both the empathizer and the target (see Fig. 1). It was hypothesized that across all conditions hand-holding would lead to pain relief in the target. We also predicted that social touch would involve shared activity in the OE system between the empathizer and the target. Building on recent studies showing that prefrontal regions including the medial and inferior frontal gyrus participate in self-regulation of pain (Diano et al., 2016; Ong, Stohler, & Herr, 2019; Petrovic & Ingvar, 2002; Seminowicz & Moayedi, 2017; Woo, Roy, Buhle, & Wager,

[1] de Waal & Aureli, 1996.

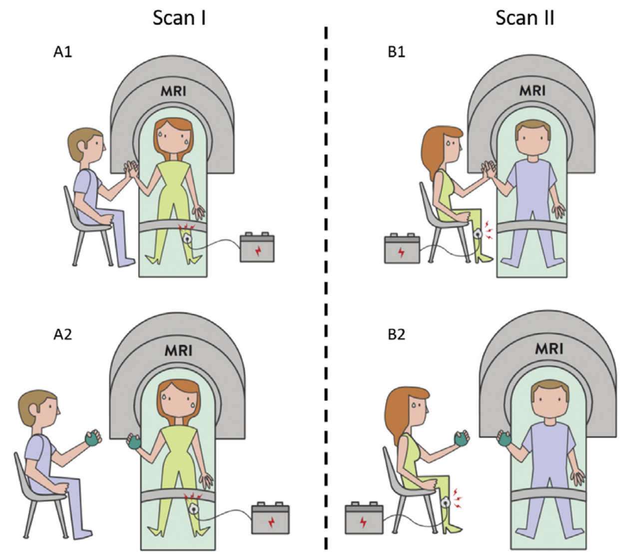

Fig. 1 – Illustration of the experimental procedure. The roles of the partners were consistent throughout the whole experiment: in one scan, the target lies inside the scanner, and in the other-the empathizer. In both scans subjects experienced all four conditions. For example, in both A1 and B1 partners experienced 'pain + human touch' while in A2 and B2 'pain + non-human touch'.

2015), we predicted that shared activation between the target and the empathizer in the OE system would be coupled with activity of self-regulation of pain regions in the target and that this activity would predict the level of pain reduction.

2. Materials and methods

2.1. *Participants*

Twenty-two couples who have been in romantic relationships for at least one year were recruited for the study. Two couples were later removed from analysis due to malfunction of the MRI scanner. Thus, the final sample included 40 participants.

All participant were at least 18 years old (male mean age: 26.05 y, SD = 2.13, female mean age: 24.4 y, SD = 2.2). Participants were recruited from the University of Haifa via advertisements, and respondents were included if they met the following inclusion criteria: (i) fluency in Hebrew; (ii) right-hand dominance (iii) no chronic or acute pain of any type; (iv) no medication use (except for oral contraceptives); (v) no history of neurological disorders, psychiatric problems, or other problems relevant to the study; (vi) no conditions that prevented scanning (e.g., a pacemaker, claustrophobia); (vii) normal or corrected-to-normal vision. Participants were screened via telephone and eligible participants were told they were participating in a study on physical pain.

No part of the study procedures or analyses was preregistered prior to the research being conducted.

2.2. *Procedure*

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. All data, code and digital materials that are necessary to replicate this study are available at: https://github.com/SANS-Lab-Haifa/Comforting-Effects-of-Social-Touch.

At the beginning of the experiment, when the couple arrived at the lab, the partners were randomly assigned to one of two roles: empathizer and target. This division was consistent throughout the whole experiment. In ten couples the female was the empathizer and the male was the target and in the other ten couples the roles were reversed.

The experiment consisted of two main conditions in a factorial design: (1) pain (pain/no-pain) and (2) touch (human touch/non-human touch) producing four condition: "pain + human touch" (referred to as the "social touch condition"), "pain + non-human touch", "no-pain + human touch" and "no-pain + non-human touch". Specifically, the target partner was inflicted with either low ('no-pain') or high ('pain') intensity heat stimuli while the empathizer partner held his/her hand ('human touch') or they both squeezed a rubber ball ('non-human touch'). Participants were instructed to hold their hands and hold the rubber ball similarly. They were asked to wrap their hand around the hand/rubber-ball until they are instructed to let go. We also asked them to try and activate the same force in both touch conditions. Pain stimuli were applied to the anterior surface of the target's right calf using the 30 mm × 30 mm Peltier surface stimulator of the Thermal Sensory Analyzer 2001 (TSA) system (TSA-2001, Medoc, Ramat-Yishai, Israel) and the intensity of pain was calibrated based on the individual's perceived pain level (see Section 2.3). Before the scanning sessions a short version of the experiment was conducted to acquaint the participants with the experimental design and the heat stimuli. Following the practice experiment, two succeeding sessions were conducted in two separate fMRI scans. In one session the task was performed while the target was inside the scanner and the empathizer sat outside the scanner, and in the other the empathizer was inside and the target was outside. The order of the scans was randomized and the two scans were conducted successively.

2.3. *Calibration of pain stimulus intensity*

Before the scanning sessions, the target partner underwent a brief test which was designed to determine the temperature of the pain stimulus to be used in the pain condition. 10-sec heat stimuli were administered to the anterior surface of the right leg, using the 30 mm × 30 mm Peltier surface stimulator. The no-pain temperature was set at 41 °C, building on studies indicating that this level is detectable but not painful (Granot & Ferber, 2005; Neziri, Curatolo, et al., 2011; Neziri, Scaramozzino, et al., 2011). The 'pain' condition intensities were calibrated for each subject to evoke a peak pain magnitude of approximately 60/100 ('pain 60'). The pain 60 procedure is a very common measurement in pain perception studies and can therefore be considered as a standard measurement. The purpose of the pain calibration was to make sure that the targets felt similar levels of pain. Finding pain 60 for each target was the way to normalize the experience between participants as much as possible. To do this, a series of 12 heat stimuli were administered in a pseudo-random order (three temperatures of 46 °C 47 °C and 48 °C; four repetitions per temperature). Following each stimulus, subjects were asked to numerically rate the pain intensity (“0” – no pain at all, “100” – maximum pain imaginable). After identifying the target’s pain level of 60, we delivered a 41 °C stimulus three times in order to ensure that the participants did indeed rate this temperature as not painful at all. All participants rated this temperature as less than a pain intensity of 10, confirming that this heat level can be used as the no-pain condition. For each couple, the empathizer was then exposed to the pain stimulus selected for their partner to introduce them to the level of pain the target would experience throughout the scanning sessions. In order to create a relatively gradual experience when the participant is inflicted with pain, a relatively slow ramping period was selected (4 sec).

2.4. *Scanning sessions*

Before the beginning of the scanning, a training session was conducted outside the scanner. Training included a short version of the task, 8 trials only, in which the participants practiced all the conditions mentioned above (Fig. 2).

Scanning consisted of two identical sessions. The order of the sessions was counterbalanced across the couples. During scanning, one of the participants was lying in the scanner while his/her partner sat near the scanner (See Fig. 1). The hand-holding/ball squeezing was carried out using the left hand of the participant sitting outside the scanner and the right hand of the participant inside the scanner. Each participant completed three functional runs, each consisting of the following conditions: pain + human touch, pain + non-human touch, no pain + human touch, no pain + non-human touch, in a counterbalanced order. As illustrated in Fig. 2, each trial consisted of the following: (1) Instructions indicating whether the target would receive a high or low pain stimulus and instructions asking the participants either to hold their partner’s hand or to squeeze a ball (6 sec); (2) Administration of the pain stimulus to the right calf (total of 26 sec; 4 sec of gradual increase in temperature from baseline to the target temperature, 20 sec of stable stimulation, and 2 sec to return to baseline); (3) A visual analogue scale (VAS). The target was asked to rate the perceived level of pain unpleasantness while, simultaneously, the empathizer was asked to rate his/her level of empathic support. For both partners the scale ranged from 0, denoting no pain unpleasantness/minimal assistance, to 100, the worst pain imaginable/maximal assistance (8 sec); (4) Instructions asking the couple to release their partner’s hand/the ball (4 sec); (5) a rest period (50 sec). Both of the subjects were exposed to the instructions and thus both of them knew the intensity of the stimulus about to be delivered. Each run was composed of eight trials, such that each condition was repeated twice in a mixed event-related paradigm. The experiment lasted almost 5 h (including 30 min break between scanning sessions) and each couple was paid a total of $150.

2.5. *Data analysis*

2.5.1. *Image acquisition*

Participants were scanned using a 3T GE scanner at the Rambam Medical Center in Haifa, Israel. Functional magnetic resonance imaging (fMRI) was carried out with a gradient echo-planar imaging (EPI) sequence of functional T2*-weighted images (TR/TE/flip angle: 2000/30/80; FOV: 217 mm; matrix size: 64 × 64) divided into 43 axial slices (thickness: 3.4 mm; gap: 0 mm) covering the whole cerebrum. Anatomical 3D sequence spoiled gradient echo (SPGR) sequences were obtained at high-resolution 1-mm slice thickness (matrix: 256 × 256; TR/TE: 8/3.1 msec).

2.5.2. *fMRI data analysis*

fMRI data were analyzed using the Statistical Parametric Mapping toolbox for Matlab (SPM8: Wellcome Trust Center for Neuroimaging, University College London, www.fil.ion.ucl.ac.uk/spm). Since interpolation was used to minimize timing errors between slices in the functional images (Henson, Büchel, Josephs, & Friston, 1998), which were then spatially realigned to the mean, coregistered with the anatomical image, normalized to the standard T1 template volume (MNI), and smoothed using an isotropic 5 mm FWHM Gaussian kernel.

The effects of pain and social touch on each participant’s brain activity were estimated using an event-related design.

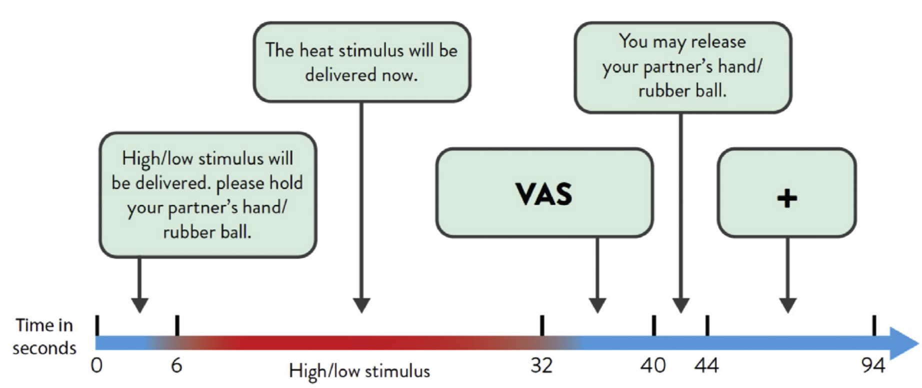

Fig. 2 – Schematic illustration of one trial.

Each phase of the trials (i.e., instructions, stimuli, responses, and fixation) was modeled separately. Stimuli in each of the experimental conditions (no pain + non-human touch; no-pain + human touch; pain + non-human touch; pain + human-touch) were modeled separately, so as to enable comparisons of the effects of pain and social touch at the group ("2nd") level (see below). Hemodynamic responses to stimuli were estimated for epochs beginning with the onset of stimulation (i.e., the beginning of the rise in temperature), and lasting till stimulation was turned off, and temperatures began to decrease. A high-pass filter with a cutoff frequency of 1/128 Hz was applied to the time series from each voxel. Hemodynamic responses to stimuli in each of the four experimental conditions were compared with hemodynamic responses during fixation, and maps of these comparisons, obtained from each of the participants, were entered into 2 × 2 ("pain"/"no pain" × "human touch"/"no human touch") model at the group level. Separate models were defined for empathizers and for target participants. All results reported here were significant both at the voxel level (corrected for multiple comparisons, i.e., pFWE <.05), and at the cluster level.

2.6. Statistical analysis

2.6.1. *Behavioral analysis*

Pain ratings provided by target participants were entered into a repeated measures ANOVA. Two within-subject factors defined the experimental condition presented in each trial, and were referred to as "type of touch" (a variable distinguishing between trials in which target participants held their partner's hand, and trials in which they squeezed a ball), and "pain" (a variable distinguishing between exposure to high and low temperatures).

2.6.2. *Imaging analysis*

The data analysis included four phases. First we carried out an initial contrast between pain versus no-pain. Activations during pain versus no-pain trials were examined by comparing trials in which target participants were exposed to high painful temperatures (pain trials) compared to trials in which they were exposed to low temperatures (no-pain trials). This phase was carried out to confirm that we replicate previous findings on pain related activation in our complex experimental design. In the second phase we explored touch related activations by comparing trials in which the empathizer and target participants held hands (human touch) with trials in which they held a ball (non-human touch). This phase included extracting the beta values derived from clusters of voxels activated in Human-touch > non-human touch contrast and carrying out follow-up t-tests to compare the beta weights in these clusters in the pain versus no pain condition both in the targets and the empathizers. In the third phase, we compared of social touch (pain + human-touch) condition to all other condition. This analysis was similar to the analysis reported recently in a paper from our lab which also examined the influences of touch on pain and neural activity (Goldstein et al., 2018). This comparison allows us to highlight the unique effect of touch on pain. We first contrasted "pain + human touch" condition with each of the other three conditions separately. A similar analysis included a contrast of "pain + non-human touch" with all other three condition. Finally, we carried out a pain × touch interaction analysis. All results reported were significant both at the voxel level (corrected for multiple comparisons, i.e., pFWE <.05), and at the cluster level).

2.6.3. *Functional connectivity*

In order to examine the self-regulatory mechanisms underlying the effects of pain relief in the target, we applied psychophysiological interaction (PPI) analysis to examine connectivity between the brain regions in the target's brain which were found to be activated in the social touch condition.

2.6.4. *Analysis of brain-behavior correlations*

To identify the relationship between social touch related activity and pain ratings we examined the correlation between neural activity found in the interaction analysis and the PPI analysis described above and the target's pain ratings. We focused on two behavioral measurements: (1) Social touch index that represents the difference between experiencing pain with or without human touch (pain + human touch subtracted from pain + non-human touch); (2) Pain index that represents the difference between experiencing touch with or without pain (no-pain + human touch subtracted from pain + human touch). This measure represents pain rating after controlling for ratings during touch in general (baseline response for touch). Both of these indices were calculated from the mean target ratings in both scans.

3. Results

3.1. Behavioral findings

The 2*2 (pain/no-pain*human-touch/non-human touch) ANOVA analysis of the target's pain rating scores revealed a significant main effect for both the touch (hand-holding/rubber-ball) and pain conditions (pain/no-pain) (type of touch: $F_{(1,19)} = 20.54$, $p < .001$, $\eta_p^2 = .52$; pain: $F_{(1,19)} = 551.86$, $p < .001$, $\eta_p^2 = .97$). As predicted, participants reported lower unpleasantness for 'human-touch' trials condition and for 'no-pain' trials. The two-way pain*touch interaction was also significant ($F_{(1,19)} = 7.27$, $p < .05$, $\eta_p^2 = .28$). Follow-up t-test, with Bonferroni correction for multiple comparisons, revealed significant differences between human-touch and non-human touch in both pain and no-pain trials ($F_{(1,19)} = 16.46$, $p < .005$, $\eta_p^2 = .46$; $F_{(1,19)} = 9.38$, $p < .01$, $\eta_p^2 = .34$, respectively), with larger differences in the pain trials, See Fig. 3.

3.2. Whole-brain analysis

3.2.1. *Main effect of pain*

In the target participants, pain > no-pain contrast yielded significant activations in several regions, including the insula and operculum bilaterally, the right IFG pars opercularis, and the left thalamus, pallidum, and putamen. In the empathizers, this contrast revealed no significant activations (Fig. 5 and Table 2).

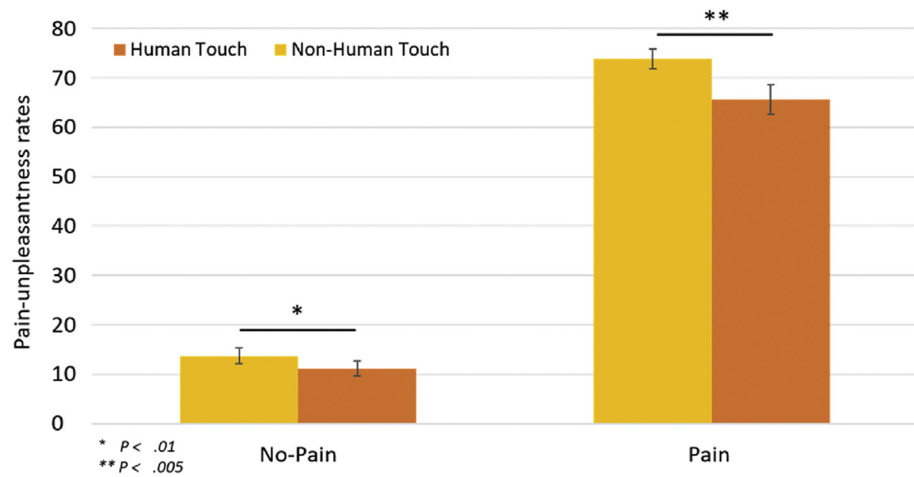

Fig. 3 – Rating of pain unpleasantness by the target partner. Vertical lines indicate standart error.

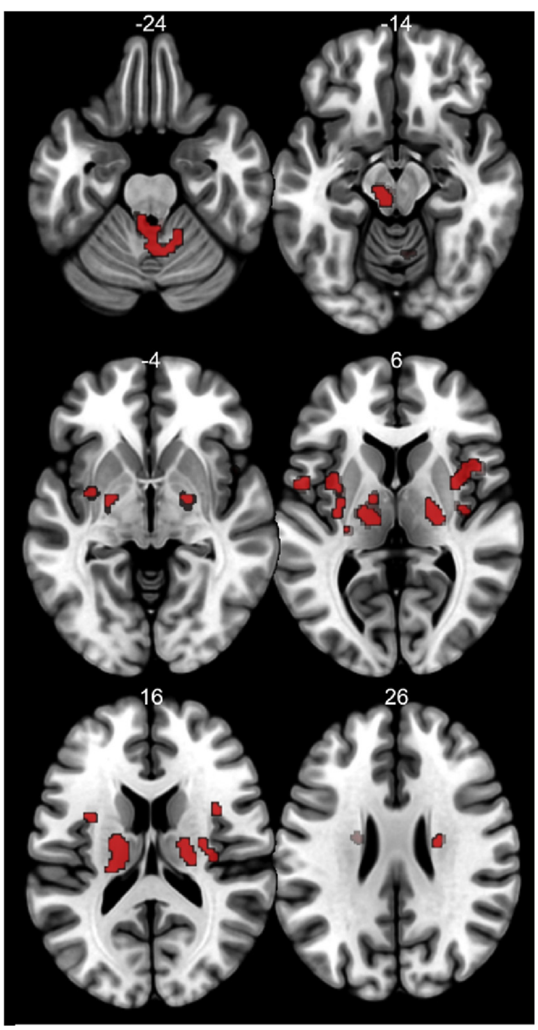

Fig. 4 – Regions more strongly activated during pain trials compared to no-pain trials among target participants.

3.2.2. *Main effect of human touch*

In the target participants, activation in left pericentral regions as well as left postcentral and precentral gyri and in the left IPL was stronger during human-touch, compared to non-human touch contrast. In the empathizers, this contrast yielded higher activations in the left postcentral and precentral gyri, and in the left IPL, the left supramarginal gyrus and superior temporal gyrus (Fig. 4 and Table 1).

To further investigate the effects of hand-holding in the target and empathizers we extracted the beta values derived from clusters of voxels activated in Human-touch > non-human touch contrast (IPL, postcentral gyrus, precentral gyrus). Follow-up t-tests revealed higher beta weights in these clusters in the pain versus no pain condition both in the targets ($t(19) = 2.98$, $p = .008$) and the empathizers ($t(19) = 2.17$, $p = .043$). These findings point that these regions were highly active in the pain condition in both partners.

3.2.3. *The comforting effect of social touch*

In order to identify regions that responded specifically to social touch during pain we compared the social touch (pain + human-touch) condition to all other condition, and the “non-human touch + pain” condition to all other conditions.

The comparison of social touch condition (human touch + pain) to all other conditions revealed significant activation in both the target and the emphasizer. Interestingly, in both partners, significant activation was observed in the left IPL and pericentral regions. In the empathizers this activation was more widespread (Fig. 6 and Table 3).

Notably, there was an overlap of 99 voxels between the clusters obtained for target participants and empathizers, which constitutes over one half of the voxels in the cluster obtained for target participants, and over one quarter of the voxels in the cluster obtained for empathizers. The analysis which examined the pain + non-human touch compared to all other conditions (in the target), revealed significant activations in the bilateral insula and the midbrain (see Table 4).

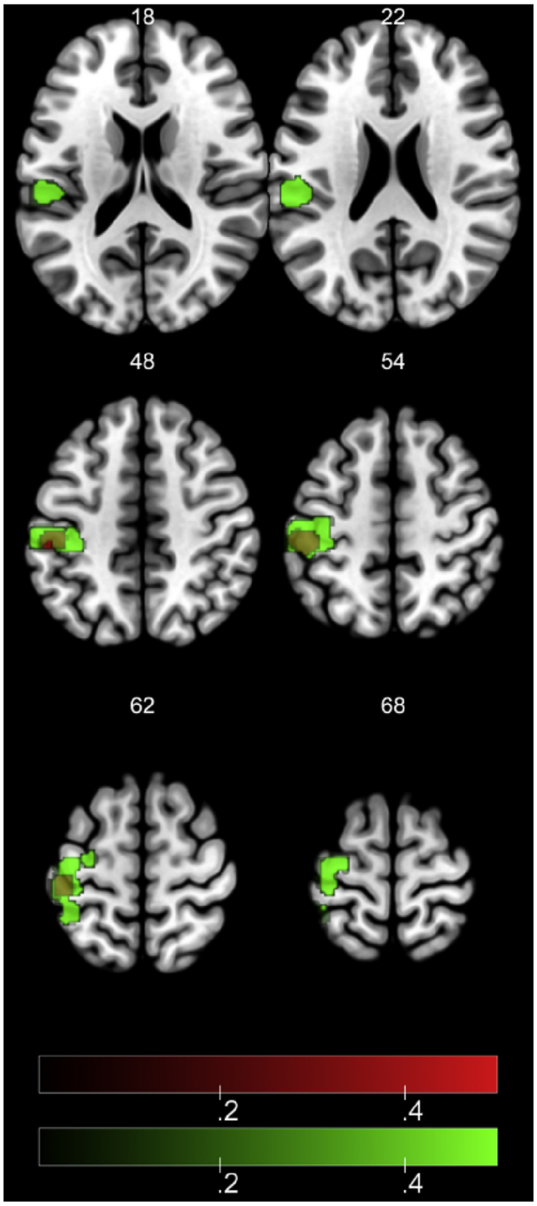

Fig. 5 – Regions more strongly activated during human touch trials compared to non-human touch trials. Red – Regions exhibiting an effect of touch among target participants; Green – regions exhibiting an effect of social touch among empathizers.

Table 1 – Anatomical location of regions more strongly activated during human touch trials compared to non-human touch trials.

Anatomical location (AAL)	x;y;z	Z	K
Empathizer, human touch > non-human touch			
Left postcentral gyrus	−40;−26;54	5.91	1011
Left precentral gyrus	−38;−20;68	5.75	
Left IPL	−58;−28;48	5.75	
Left supramarginal gyrus	−50;−24;18	5.67	197
Left STG	−58;−30;22	5.32	
Target, human touch > non-human touch			
Left IPL	−54;−26;48	5.66	267
Left postcentral gyrus	−52;−28;58	5.56	

Table 2 – Anatomical location of regions more strongly activated during pain trials compared to no-pain trials among target participants.

Anatomical location (AAL)	x;y;z	Z	K
Target, pain > no-pain			
Right insula	36;6;12	5.56	134
Right IFG pars opercularis	46;10;4	4.92	
Left insula	−34;4;10	5.54	108
Left rolandic operculum	−52;2;6	5.36	36
Left pallidum	20;−6;−2	5.33	189
Left cerebellum	−4;−42;−28	5.25	233
Left thalamus	−18;−20;14	5.16	310
Left parahippocampal gyrus	−8;−24;−12	5.19	46
Right rolandic operculum	36;−20;20	5.12	90
Left putamen	−32;−10;6	4.77	

Finally, we conducted a two-way pain × touch interaction and found no significant cluster that reached the significance threshold.

3.3. *ROI analyses*

Regions of interest (ROIs) were defined in the IPL and pericentral clusters obtained from the "social-touch (pain + human-touch) > all" contrast described above, for both target participants and empathizers. This was done in order to enable the examination of correlations between activation measured among target participants and activation measured among their partners. This correlation was significant in the social touch condition ($r = .51$, $p < .001$, see Fig. 7).

3.3.1. *Brain-behavior correlations*

The correlations between beta values extracted from the IPL and the pain and social touch indices were not significant.

3.4. *PPI analysis*

PPI analysis with the left IPL (obtained from the "social touch > all" contrast) as the seed region, was conducted for the target participants. This was done in order to identify regions that might have been involved in the mitigating effect of social touch on the perceived pain of the target participant. When an uncorrected threshold of $p_{unc.} < .001$ was applied, this analysis yielded a significant cluster in the right superior dorsomedial prefrontal cortex (dmPFC, [x,y,z: 8,50,42]) with positive connectivity pattern (see Fig. 8).

Correlations between activation in the dmPFC and pain indices were examined in order to determine the contribution of this region to pain alleviation. These analyses revealed a significant negative correlation ($r = -.47$ $p = .038$, see Fig. 9) between activity in the dmPFC and the pain index (after omission of one participant with extreme activation in the dmPFC – 2.5 SD above the mean), suggesting that, during social touch, higher activations in the dmPFC predicts less pain. To ensure that this correlation was specific to the social touch condition we further carried out a similar analysis in the other conditions and found no significant correlations ($p > .05$).

No significant correlation was found between dmPFC activation and the social touch index.

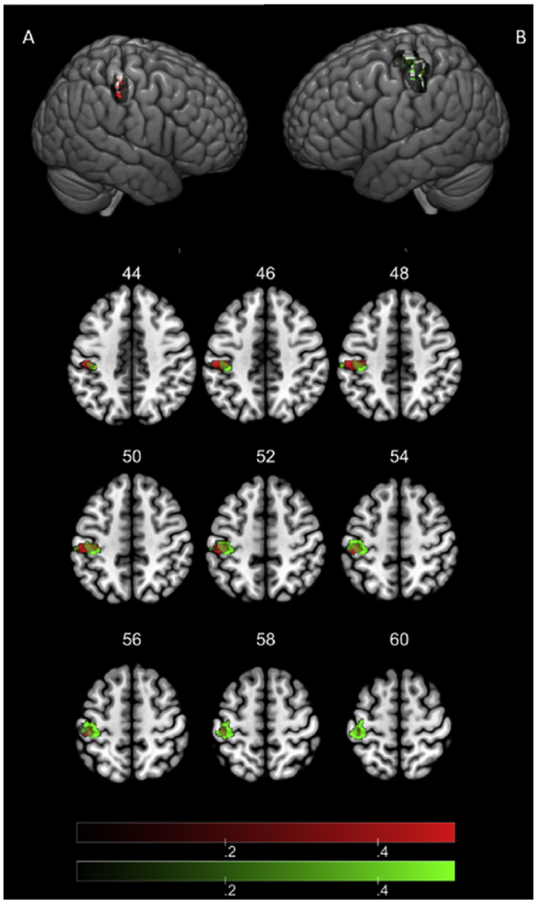

Fig. 6 – Regions more strongly activated during pain + human touch trials, compared to all other trials, in both the target (A) and the empathizer (B).

Table 3 – Anatomical location of regions more strongly activated during pain+human touch trials, compared to all other trials.

Anatomical location (AAL)	x;y;z	Z	K
Empathizers, pain + human-touch > all			
Left postcentral gyrus	−40;−28;54	5.55	394
Left precentral gyrus	−38;−20;68	5.01	
Left postcentral gyrus	−44;−26;46	4.99	
Left precentral gyrus	−30;−16;68	4.95	
Left IPL	−58;−28;50	4.90	
Left precentral gyrus	−38;−18;60	4.70	
Target, pain + human-touch > all			
Left IPL	−46;−26;46	5.39	180

Table 4

Anatomical location (AAL)	x;y;z	Z	K
Target, pain + non-human touch > all			
Left insula	−34;4;12	5.38	44
Right insula	38;6;14	5.38	39
Midbrain	10;−26;−14	5.00	49

4. Discussion

Interpersonal touch is a common behavior, often used to reduce distress in others (de Waal & Aureli, 1996). However, the mechanisms that contribute to the pain relief induced by touch have not been fully explored before. We show that hand-holding diminishes pain, and, importantly, we demonstrate shared neural activation between the target and the empathizer in the IPL, a region that was found to be activated during tasks that require imitation, coordination and synchronizing between the participants' responses.

Analysis of the reported pain ratings indicates that hand-holding has an alleviating effect on pain ratings during thermal stimulation. Our results also indicate that social touch in the form of hand-holding is more effective than merely holding an object, confirming that human touch and not any type of touch reduces pain. Accumulating evidence suggests that different types of social touch reduce stress and anxiety (Coan et al., 2006; Ditzen et al., 2007; Grewen et al., 2003; Kawamichi et al., 2015), physical pain (Goldstein et al., 2018; Krahé et al., 2014; Liljencrantz et al., 2017; Master et al., 2009) and even feelings of social exclusion (Von Mohr, Kirsch, & Fotopoulou, 2017). The current findings are in line with these studies and stress the contribution of hand-holding to the relief of physical pain. In contrast with theories that emphasize the role of the mechanical component of touch in pain reduction (Melzack & Wall, 1965), our study highlights the specific effect of skin-to-skin touch delivered by a significant other in pain alleviation. Notably, most of the research that studied the effect of pain alleviation caused by a significant other focused mainly on visual input, using the presence of the romantic partner, pictures or direct visual input of him/her (Eisenberger et al., 2011; Krahé et al., 2014; Younger, Aron, Parke, Chatterjee, & Mackey, 2010). In our study, the effect of pain relief was achieved using only touch and was significant despite the fact that the target partner could not see the empathizer. Moreover, human touch was also effective in reduction unpleasantness during neutral stimuli. These findings together imply that, like visual input, touch can also be a main component in of social comforting. Given that touch is a channel for communicating emotions including love and sympathy (Hertenstein et al., 2006; Kirsch et al., 2018). It is thus possible that one mechanism by which touch diminishes pain is by communicating emotions. The empathizer communicates positive emotions such as warmth, love and sympathy while the target communicates her/his distress. This emotional sharing is a form of co-regulation, as the target experiences the empathy felt by the empathizer and which allows increasing sense of connectedness and may result in pain regulation.

To explore specific social touch-related activity we compared the brain activity during the social touch condition (pain + human-touch) to all the other control conditions. This analysis allowed us to examine the brain activation in the condition of interest while controlling for the effects of non-human touch and pain. The results revealed that in both the target and the empathizer the IPL was active during the social touch condition. Furthermore, the activity of the IPL of the empathizer and the target participants was significantly

Fig. 7 – Correlation between the targets' and the empathizers' clusters activations obtained from "pain + human touch" condition.

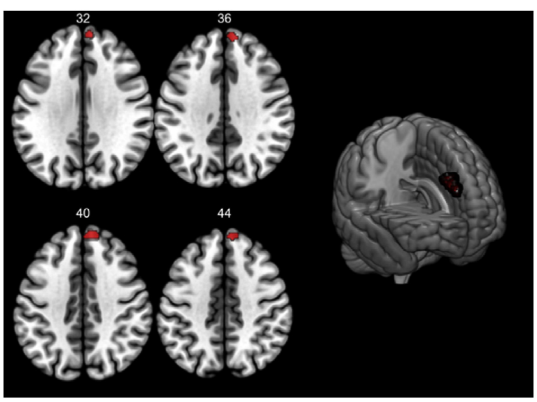

Fig. 8 – Cluster found in the PPI analysis with the left IPL and pericentral regions as seed region in the target's brain.

correlated. The literature links IPL activity to sensory processing and evaluation of thermal noxious stimuli (Duerden & Albanese, 2013). Interestingly, the IPL has a crucial role not only in evaluation of felt pain but also in the evaluation of observed pain. Previous studies that focus on neural activation while observing others' pain, have consistently shown activations of the IPL in the observer's brain. These studies attribute this activation to empathy of the observer towards the person experiencing pain and regard it as a plausible trigger for prosocial behaviors (Decety & Lamm, 2006; Jackson & Decety, 2004; Singer et al., 2004). According to the perception-action model of empathy (Preston and De Waal, 2007), during the perception of vicarious pain, a shared neural representation which relies on the IPL and the IFG is activated, allowing the observer sharing the pain experience of the target through the mirroring of such pain in his/her own system.

Research demonstrates increased activity in the IPL during both motor (Cacioppo et al., 2014) and emotional (Nummenmaa, Hirvonen, Parkkola, & Hietanen, 2008) synchronization. Importantly, activation in the IPL is reported in tasks that require communication of social information. For example, Schippers, Roebroeck, Renken, Nanetti, and Keysers (2010) highlighted the importance of the IPL in decoding social information flow during a game of charades. The authors demonstrated that during trials of interpretation only, the guesser's IPL was synchronized with the gesturer's brain activity. In line with this, Anders, Heinzle, Weiskopf, Ethofer, and Haynes (2011) have demonstrated that during an ongoing simultaneous facial communication task, a 'shared social network' is activated in both the perceiver's and the sender's brain.

Taking into account the mentioned role of the IPL in pain perception, empathy for pain and mirroring, it is reasonable to assume that the observed shared activation in the IPL enables shared experience of the painful sensation in both the target and the empathizer.

Notably, Kilner, Friston, and Frith (2007) suggested that using predictive coding, the IPL is involved in inferring other's intentions and thought from their observed action (i.e., the 'inverse model'). This theoretical framework has been expanded to include the idea that shared experience and social interactions can influence our predictions regarding the other (Fotopoulou & Tsakiris, 2017; Ishida, Suzuki, & Grandi, 2015). Moreover, recent studies suggest that not only can social interaction modulate our predictions relating to the environment, but it also enables pain relief by using the other's reactions as a predictive signal that allows reevaluation of the current aversive stimulus (see Fauchon et al., 2019 and von Mohr et al., 2018, and Krahé, Springer, Weinman, & Fotopoulou, 2013 for a comprehensive review). These

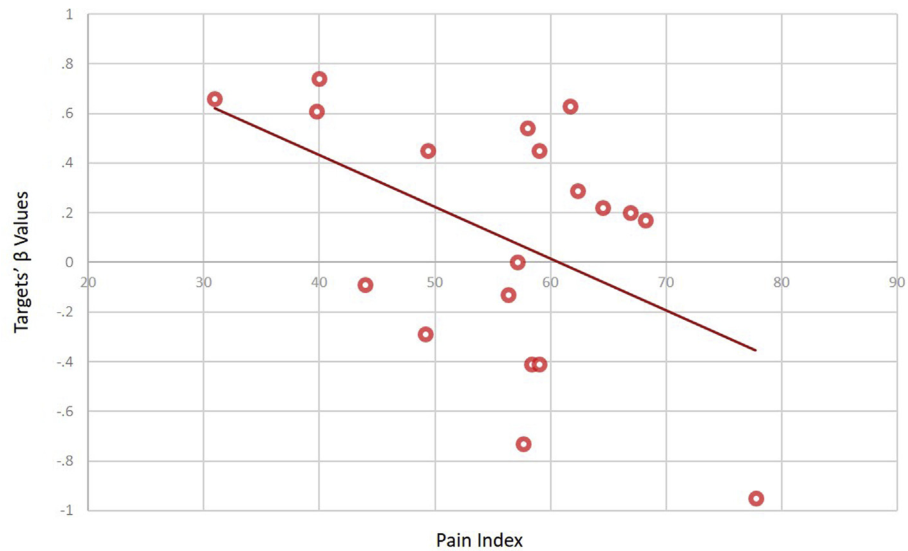

Fig. 9 – Correlation between target's beta values, extracted from the dorsomedial prefrontal cortex and pain index.

findings, together with evidence pointing that the IPL is a central in the attentional network (Chambers, Payne, Stokes, & Mattingley, 2004; Hopfinger, Buonocore, & Mangun, 2000; Shapiro & Hillstrom, 2002), suggest that the observed shared activation in both the target's and emphasizer's IPL represents a shift of attention toward each other, which enhances the predictions regarding the other's acts and intention. Notably, the complementary analysis of non-human touch + pain in the target revealed significant activation in the midbrain and bilateral insula, regions that are repeatedly found to be activated during physical pain (Almeida, Roizenblatt, & Tufik, 2004; Millan, 1999). Collectively, it may be argued that non-human touch does not reduce pain or activation in pain related regions. On the other hand, human touch during pain is associated with activation in regions related to shared emotions and prediction regarding others.

It is important to note that the pain*Touch interaction analysis did not reveal significant activations. One possible explanation may be related to the difference in brain activity associated with pain versus touch. While the pain conditions were associated with strong brain activations, the brain activations during the touch condition were more subtle. Thus, carrying out this type of contrast may eliminate activations that are specific to the social touch condition.

The results of the PPI analysis in the target participants demonstrate significant interaction between the IPL and the dmPFC. In their comprehensive review on pain and social support, Krahé et al. (2013) suggest that social support during pain encourages reassessment of the threat stimuli and the environment and thus influences the salience of the stimulus. According to this view, external support motivates a new evaluation of the pain and may influence the pain perception and related action plans. Building on this framework, it is possible that the coupling between the IPL and the dmPFC observed in the current study represents an interpersonal process of emotion regulation. Importantly, activity in the dmPFC predicted lower levels of pain in the target, suggesting, this region contributes to regulating the level of pain of the target. The superior dmPFC is generally considered to encompass the lateral and the superior portions of Brodmann area 9, the whole of area 8 or only its superior portion (Brodmann, 1910). Several functional studies have indicated that this region is activated in emotion regulation paradigms (Frank et al., 2014). Previous studies have highlighted the importance of this region in emotion regulation and in the ability to confront negative and aversive situations (Eippert et al., 2007; Etkin, Büchel, & Gross, 2015; Ochsner & Barrett, 2001). One major strategy to cope with aversive stimuli is reappraisal, a high-level cognitive strategy that influences negative emotion by reformulating the meaning of the observed stimulus. This process involves working memory, goal representation and selective attention and was associated with activity in the dmPFC (Beauregard, Lévesque, & Bourgouin, 2001; Buhle et al., 2014; Eippert et al., 2007; Frank et al., 2014; Ochsner & Barrett, 2001; Ochsner & Gross, 2004,

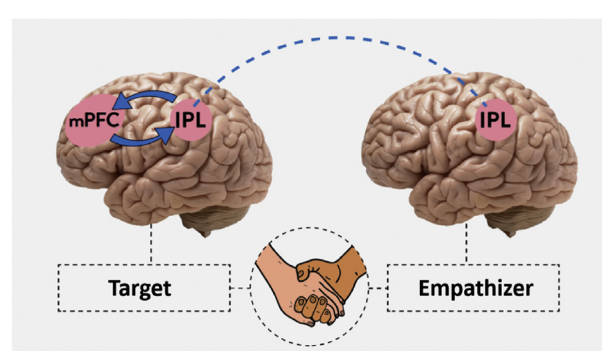

Fig. 10 – Proposed mechanism of the effect of touch on pain reduction. During pain, a shared interbrain network between the empathizer and the target up-regulates emotion regulation processing in the target and down-regulates her/his pain.

2008). Taken together with the aforementioned correlation between activation in the target participants and their partners, our results provide support for the hypothesis of Krahé et al. (2013) that social touch may cause reduction of pain through active reappraisal of the painful situation (See our suggested model in Fig. 10).

Considering that the dmPFC has also been associated with mental state attribution, another possibility is that the dmPFC activity is evident during social touch because the target attempts to take the perspective of the empathizer. Indeed, recent studies demonstrate that the effectiveness of support correlates with the perceived empathic abilities of the empathizer (Goldstein, Shamay-Tsoory, Yellinek & Weissman-Fogel, 2016; Hurter, Paloyelis, Amanda, & Fotopoulou, 2014; Sambo, Howard, Kopelman, Williams, & Fotopoulou, 2010) and with her/his expectation of upcoming social support (Krahé et al., 2014, 2016). Thus, it is plausible that the dmPFC activation also represents the attempt of the target to appreciate the empathizer's ability to provide support.

Notably, while no correlation was found between the reported pain relief and the IPL activation, a negative correlation was found between the dmPFC activation and the pain index. This correlation was specific to the social touch condition, further confirming that dmPFC activity correlates with levels of pain only during social touch. These results emphasize that the correlated activation in the IPL of both partners does not directly generate pain relief, rather the involvement of the dmPFC is required for diminishing the levels of pain.

It should be noted that in contrast to these results, Coan et al. (2006), found that hand-holding during threat attenuated threat-related neural activation in areas implicated in the regulation of emotion (right dorsolateral prefrontal cortex) in the target. It is possible that the differences between the results found in these studies are related to the type of the paradigms in each study. Whereas in Coan et al.'s study social touch was provided during the expectation of a painful shock, in the current study the human touch was given during actual physical thermal pain. In other words, while Coan's study focused more on the effects of touch on the expectation of pain, highlighting components such as stress, arousal and the ability to predict future pain, our study examined the influences of social touch on coping with actual painful. It may be speculated that in the initial phase of social touch, when expecting pain, there is decrease in frontal activity, while during pain itself there is increase in frontal activity.

Given the complexity of the dual-brain design used in the current study, we also examined basic activity in touch and pain networks in the target and the empathizer. In line with previous studies, our results indicate that both human touch (as compared to non-human touch) and pain stimuli (as compared to no-pain stimuli) activate the expected neural regions in both the target and the empathizer. Human touch was associated with activations in pericentral regions which relate to skin-to-skin touch, grasping and skin-to-skin sensation (see Castiello, 2005 and Keysers, Kaas, & Gazzola, 2010 reviews on these regions) in both partners, while the infliction of pain activated pain related regions including the insula, thalamus and inferior frontal gyrus in the target participant (Derbyshire & Jones, 1998; Hsieh et al., 1996; Ploghaus, 1999). In contrast with previous studies that show pain related activity (ACC, AI) during the observation of pain of the other (e.g., Singer et al., 2004), the contrast of pain > no pain in the empathizers revealed no significant activations. It should be noted that in our study the empathizer was not a passive observer of the situation but played an active role in relieving pain. The "second-person" neuroscience approach suggested by Schilbach et al. (2013) holds that social behavior may involve different processes when one interacts with others rather than merely observes them. Indeed, most paradigms in social neuroscience are based on computerized tasks where participants passively observe decontextualized social stimuli such as still pictures of facial expressions or an isolated scene depicting a social interaction (Shamay-Tsoory and Mendelsohn, 2019). Thus, it is possible that the activity in the ACC and AI reported in previous studies is related to designs that involve passive viewing of the other pain.

The current study used a new approach for understanding social interactions that involve real physical interaction. Despite our attempt to create a controlled design with balanced conditions there are some limitations that need to acknowledge. First, we did not measure the force of the hand-holding. This is important because the IPL is also involved in self generating movement such as grasping (Castiello, 2005; Castiello et al., 2000). Although we instructed the subject to use the same force in both touch conditions one may argue that the reported activity in the IPL is explained by mere mutual grasping. Nonetheless, considering that this region was active in the contrast that compared social touch to all other conditions (grasping a hand or grasping a ball), it is highly unlikely that the observed activity in the IPL could be explained by grasping alone. A second limitation relates to the essence of dual brain analysis as compared to synchronization. Unlike hyperscanning studies that use simultaneous scans of pairs, in the current study participants were scanned serially. Although this design does not allow measuring inter-brain synchrony in real-time, it allows revealing brain activations associated with the comforting effect of human touch in both the target and the empathizer.

Taking into account these limitation, our study shows that skin-to-skin touch of a significant other, in the form of hand-holding, can reduce the intensity of perceived pain. In contrast to previous studies on social touch, we examined real-life social touch in both the target and the empathizer, a paradigm that allowed us to investigate the interactions between both partners. We suggest that the analgesic effect of human touch relies on the correlated brain activity of the target and the empathizer during social touch. We also propose that the observed activity in the medial frontal gyrus of the target partner, which is positively coupled with activation in the IPL (which itself is correlated with activation in the empathizer), suggests that interpersonal touch can aid the target participant engage in emotion regulation. These findings challenge the traditional models of empathy and suggest that applying interactive paradigms may allow developing models that take into account both the empathizer and the target of pain.

Open practices

The study in this article earned an Open Data badge for transparent practices. Materials and data for the study are available at https://github.com/SANS-Lab-Haifa/Comforting-Effects-of-Social-Touch.

Acknowledgments

This research was supported by the Binational Science Foundation (BSF) Grant 2015068. The authors thank Amitay Ron and Bar Izkovich for assisting in running the study, Daniela Cohen, Naama Mayseless and Lee Bareket-Kisler for assisting in data analysis and Nir Adi who created the illustrations.

REFERENCES

Almeida, T. F., Roizenblatt, S., & Tufik, S. (2004). Afferent pain pathways: A neuroanatomical review. *Brain Research*. https://doi.org/10.1016/j.brainres.2003.10.073.

Anders, S., Heinzle, J., Weiskopf, N., Ethofer, T., & Haynes, J. D. (2011). Flow of affective information between communicating brains. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2010.07.004.

Apkarian, A. V., Bushnell, M. C., Treede, R. D., & Zubieta, J. K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain*. https://doi.org/10.1016/j.ejpain.2004.11.001.

Batson, C. D. (2009). These things called empathy: Eight related but distinct phenomena. In *The social neuroscience of empathy*. https://doi.org/10.7551/mitpress/9780262012973.003.0002.

Beauregard, M., Lévesque, J., & Bourgouin, P. (2001). Neural correlates of conscious self-regulation of emotion. *The Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.21-18-j0001.2001.

Brodmann, K. (1910). Localisation in the cerebral cortex the. *The Journal of Nervous and Mental Disease*. https://doi.org/10.1097/00005053-191012000-00013.

Buhle, J. T., Silvers, J. A., Wage, T. D., Lopez, R., Onyemekwu, C., Kober, H., et al. (2014). Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bht154.

Cacioppo, S., Zhou, H., Monteleone, G., Majka, E. A., Quinn, K. A., Ball, A. B., et al. (2014). You are in sync with me: Neural correlates of interpersonal synchrony with a partner. *Neuroscience*. https://doi.org/10.1016/j.neuroscience.2014.07.051.

Castiello, U. (2005). The neuroscience of grasping. *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn1744.

Castiello, U., Bennett, K. M., Egan, G. F., Tochon-Danguy, H. J., Kritikos, A., & Dunai, J. (2000). Human inferior parietal cortex "programs" the action class of grasping. *Cognitive Systems Research*. https://doi.org/10.1016/S1389-0417(99)00011-X.

Chambers, C. D., Payne, J. M., Stokes, M. G., & Mattingley, J. B. (2004). Fast and slow parietal pathways mediate spatial attention. *Nature Neuroscience*. https://doi.org/10.1038/nn1203.

Coan, J. A., Schaefer, H. S., & Davidson, R. J. (2006). Lending a hand: Social regulation of the neural response to threat. *Psychological Science*. https://doi.org/10.1111/j.1467-9280.2006.01832.x.

de Waal, F. B. M., & Aureli, F. (1996). Consolation, reconciliation, and a possible cognitive difference between macaques and chimpanzees. In *Reaching into thought: The minds of the great apes*. Cambridge University Press.

Decety, J., & Lamm, C. (2006). Human empathy through the lens of social neuroscience. *TheScientificWorldJournal*. https://doi.org/10.1100/tsw.2006.221.

Derbyshire, S. W. G., & Jones, A. K. P. (1998). Cerebral responses to a continual tonic pain stimulus measured using positron emission tomography. *Pain*. https://doi.org/10.1016/S0304-3959(98)00034-7.

Diano, M., D'Agata, F., Cauda, F., Costa, T., Geda, E., Sacco, K., et al. (2016). Cerebellar clustering and functional connectivity during pain processing. *The Cerebellum*. https://doi.org/10.1007/s12311-015-0706-4.

Dibiase, R., & Gunnoe, J. (2004). Gender and culture differences in touching behavior. *Journal of Social Psychology*. https://doi.org/10.3200/SOCP.144.1.49-62.

Ditzen, B., Neumann, I. D., Bodenmann, G., von Dawans, B., Turner, R. A., Ehlert, U., et al. (2007). Effects of different kinds of couple interaction on cortisol and heart rate responses to stress in women. *Psychoneuroendocrinology*. https://doi.org/10.1016/j.psyneuen.2007.03.011.

Duerden, E. G., & Albanese, M. C. (2013). Localization of pain-related brain activation: A meta-analysis of neuroimaging data. *Human Brain Mapping*. https://doi.org/10.1002/hbm.21416.

Eippert, F., Veit, R., Weiskopf, N., Erb, M., Birbaumer, N., & Anders, S. (2007). Regulation of emotional responses elicited by threat-related stimuli. *Human Brain Mapping*. https://doi.org/10.1002/hbm.20291.

Eisenberger, N. I., Master, S. L., Inagaki, T. K., Taylor, S. E., Shirinyan, D., Lieberman, M. D., et al. (2011). Attachment figures activate a safety signal-related neural region and reduce pain experience. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1108239108.

Etkin, A., Büchel, C., & Gross, J. J. (2015). The neural bases of emotion regulation. *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn4044.

Fauchon, C., Faillenot, I., Quesada, C., Meunier, D., Chouchou, F., Garcia-Larrea, L., et al. (2019). Brain activity sustaining the modulation of pain by empathetic comments. *Scientific Reports*. https://doi.org/10.1038/s41598-019-44879-9.

Fotopoulou, A., & Tsakiris, M. (2017). Mentalizing homeostasis: The social origins of interoceptive inference. *Neuropsychoanalysis*. https://doi.org/10.1080/15294145.2017.1294031.

Frank, D. W., Dewitt, M., Hudgens-Haney, M., Schaeffer, D. J., Ball, B. H., Schwarz, N. F., et al. (2014). Emotion regulation: Quantitative meta-analysis of functional activation and deactivation. *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2014.06.010.

Gallace, A., & Spence, C. (2010). The science of interpersonal touch: An overview. *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2008.10.004.

Garcia-Larrea, L., Frot, M., & Valeriani, M. (2003). Brain generators of laser-evoked potentials: From dipoles to functional significance. *Neurophysiologie Clinique*. https://doi.org/10.1016/j.neucli.2003.10.008.

Goldstein, P., Shamay-Tsoory, S. G., Yellinek, S., & Weissman-Fogel, I. (2016). Empathy Predicts an Experimental Pain Reduction During Touch. *J Pain, 17*(10), 1049–1057.

Goldstein, P., Weissman-Fogel, I., Dumas, G., & Shamay-Tsoory, S. G. (2018). Brain-to-brain coupling during handholding is associated with pain reduction. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1703643115.

Granot, M., & Ferber, S. G. (2005). The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: A prospective study. *The Clinical Journal of Pain*. https://doi.org/10.1097/01.ajp.0000135236.12705.2d.

Grewen, K. M., Anderson, B. J., Girdler, S. S., & Light, K. C. (2003). Warm partner contact is related to lower cardiovascular reactivity. *Behavioral Medicine*. https://doi.org/10.1080/08964280309596065.

Harbaugh, W. T., Mayr, U., & Burghart, D. R. (2007). Neural responses to taxation and voluntary giving reveal motives for charitable donations. *Science*. https://doi.org/10.1126/science.1140738.

Henson, R., Büchel, C., Josephs, O., & Friston, K. (1998). *The slice-timing problem in event-related fMRI*. Poster Presented at the 5th International Conference on Functional Mapping of the Human Brain, 1998.

Hertenstein, M. J., Keltner, D., App, B., Bulleit, B. A., & Jaskolka, A. R. (2006). Touch communicates distinct emotions. *Emotion*. https://doi.org/10.1037/1528-3542.6.3.528.

Hopfinger, J. B., Buonocore, M. H., & Mangun, G. R. (2000). The neural mechanisms of top-down attentional control. *Nature Neuroscience*. https://doi.org/10.1038/72999.

Hsieh, J. C., Ståhle-Bäckdahl, M., Hägermark, Ö., Stone-Elander, S., Rosenquist, G., & Ingvar, M. (1996). Traumatic nociceptive pain activates the hypothalamus and the periaqueductal gray: A positron emission tomography study. *Pain*. https://doi.org/10.1016/0304-3959(95)00129-8.

Hurter, S., Paloyelis, Y., Amanda, A. C., & Fotopoulou, A. (2014). Partners' empathy increases pain ratings: Effects of perceived empathy and attachment style on pain report and display. *Journal of Pain*. https://doi.org/10.1016/j.jpain.2014.06.004.

Inagaki, T. K., & Eisenberger, N. I. (2012). Neural correlates of giving support to a loved one. *Psychosomatic Medicine*. https://doi.org/10.1097/PSY.0b013e3182359335.

Ishida, H., Suzuki, K., & Grandi, L. C. (2015). Predictive coding accounts of shared representations in parieto-insular networks. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2014.10.020.

Jackson, P. L., & Decety, J. (2004). Motor cognition: A new paradigm to study self-other interactions. *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2004.01.020.

Jakubiak, B. K., & Feeney, B. C. (2016). Keep in touch: The effects of imagined touch support on stress and exploration. *Journal of Experimental Social Psychology*. https://doi.org/10.1016/j.jesp.2016.04.001.

Jones, S. E., & Yarbrough, A. E. (1985). A naturalistic study of the meanings of touch. *Communication Monographs*. https://doi.org/10.1080/03637758509376094.

Kawamichi, H., Kitada, R., Yoshihara, K., Takahashi, H. K., & Sadato, N. (2015). Interpersonal touch suppresses visual processing of aversive stimuli. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2015.00164.

Keysers, C., Kaas, J. H., & Gazzola, V. (2010). Somatosensation in social perception. *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn2833.

Kilner, J. M., Friston, K. J., & Frith, C. D. (2007). Predictive coding: An account of the mirror neuron system. *Cognitive Processing*. https://doi.org/10.1007/s10339-007-0170-2.

Kirsch, L. P., Krahé, C., Blom, N., Crucianelli, L., Moro, V., Jenkinson, P. M., et al. (2018). Reading the mind in the touch: Neurophysiological specificity in the communication of emotions by touch. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2017.05.024.

Krahé, C., Drabek, M. M., Paloyelis, Y., & Fotopoulou, A. (2016). Affective touch and attachment style modulate pain: A laser-evoked potentials study. *Philosophical Transactions of the Royal Society B: Biological Sciences*. https://doi.org/10.1098/rstb.2016.0009.

Krahé, C., Paloyelis, Y., Condon, H., Jenkinson, P. M., Williams, S. C. R., & Fotopoulou, A. (2014). Attachment style moderates partner presence effects on pain: A laser-evoked potentials study. *Social Cognitive and Affective Neuroscience*. https://doi.org/10.1093/scan/nsu156.

Krahé, C., Springer, A., Weinman, J. A., & Fotopoulou, A. (2013). The social modulation of pain: Others as predictive signals of salience – A systematic review. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2013.00386.

Lamm, C., Decety, J., & Singer, T. (2011). Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2010.10.014.

Liljencrantz, J., Strigo, I., Ellingsen, D. M., Krämer, H. H., Lundblad, L. C., Nagi, S. S., et al. (2017). Slow brushing reduces heat pain in humans. *European Journal of Pain*. https://doi.org/10.1002/ejp.1018.

Masten, C. L., Morelli, S. A., & Eisenberger, N. I. (2011). An fMRI investigation of empathy for "social pain" and subsequent prosocial behavior. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2010.11.060.

Master, S. L., Eisenberger, N. I., Taylor, S. E., Naliboff, B. D., Shirinyan, D., & Lieberman, M. D. (2009). A picture's worth: Partner photographs reduce experimentally induced pain. *Psychological Science*. https://doi.org/10.1111/j.1467-9280.2009.02444.x.

Mathur, V. A., Harada, T., Lipke, T., & Chiao, J. Y. (2010). Neural basis of extraordinary empathy and altruistic motivation. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2010.03.025.

Melzack, R., & Wall, P. D. (1965). Pain mechanisms: A new theory. *Science*. https://doi.org/10.1126/science.150.3699.971.

Millan, M. J. (1999). The induction of pain. *Progress in Neurobiology*.

von Mohr, M., Krahé, C., Beck, B., & Fotopoulou, A. (2018). The social buffering of pain by affective touch: A laser-evoked potential study in romantic couples. *Social Cognitive and Affective Neuroscience*. https://doi.org/10.1093/scan/nsy085.

Neziri, A. Y., Curatolo, M., Nüesch, E., Scaramozzino, P., Andersen, O. K., Arendt-Nielsen, L., et al. (2011a). Factor analysis of responses to thermal, electrical, and mechanical painful stimuli supports the importance of multi-modal pain assessment. *Pain*. https://doi.org/10.1016/j.pain.2011.01.047.

Neziri, A. Y., Scaramozzino, P., Andersen, O. K., Dickenson, A. H., Arendt-Nielsen, L., & Curatolo, M. (2011b). Reference values of mechanical and thermal pain tests in a pain-free population. *European Journal of Pain*. https://doi.org/10.1016/j.ejpain.2010.08.011.

Nummenmaa, L., Hirvonen, J., Parkkola, R., & Hietanen, J. K. (2008). Is emotional contagion special? An fMRI study on neural systems for affective and cognitive empathy. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2008.08.014.

Ochsner, K. N., & Barrett, L. F. (2001). A multiprocess perspective on the neuroscience of emotion. In *Emotions: Currrent issues and future directions*. https://doi.org/10.1017/CBO9781107415324.004.

Ochsner, K. N., & Gross, J. J. (2004). Thinking makes it so: A social cognitive neuroscience approach to emotion regulation. *Handbook of Selfregulation Research Theory and Applications*. https://doi.org/10.1038/386028a0.

Ochsner, K. N., & Gross, J. J. (2008). Cognitive emotion regulation: Insights from social cognitive and affective neuroscience. *Current Directions in Psychological Science*. https://doi.org/10.1111/j.1467-8721.2008.00566.x.

Ong, W. Y., Stohler, C. S., & Herr, D. R. (2019). Role of the prefrontal cortex in pain processing. *Molecular Neurobiology*. https://doi.org/10.1007/s12035-018-1130-9.

Peled-Avron, L., Goldstein, P., Yellinek, S., Weissman-Fogel, I., & Shamay-Tsoory, S. G. (2018). Empathy during consoling touch is modulated by mu-rhythm: An EEG study. *Neuropsychologia, 116*, 68–74.

Petrovic, P., & Ingvar, M. (2002). Imaging cognitive modulation of pain processing. *Pain*. https://doi.org/10.1016/s0304-3959(01)00467-5.

Ploghaus, A. (1999). Dissociating pain from its anticipation in the human brain. *Science*. https://doi.org/10.1126/science.284.5422.1979.

Preston, S. D. (2007). A perception-action model for empathy. In *Empathy in mental illness*. https://doi.org/10.1017/CBO9780511543753.024.

Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. *Annual Review of Neuroscience*. https://doi.org/10.1146/annurev.neuro.27.070203.144230.

Sambo, C. F., Howard, M., Kopelman, M., Williams, S., & Fotopoulou, A. (2010). Knowing you care: Effects of perceived empathy and attachment style on pain perception. *Pain*. https://doi.org/10.1016/j.pain.2010.08.035.

Schilbach, L., Timmermans, B., Reddy, V., Costall, A., Bente, G., Schlicht, T., et al. (2013). Toward a second-person neuroscience. *Behavioral and Brain Sciences, 36*(4), 393–414. https://doi.org/10.1017/S0140525X12000660.

Schippers, M. B., Roebroeck, A., Renken, R., Nanetti, L., & Keysers, C. (2010). Mapping the information flow from one brain to another during gestural communication. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1001791107.

Seminowicz, D. A., & Moayedi, M. (2017). The dorsolateral prefrontal cortex in acute and chronic pain. *Journal of Pain*. https://doi.org/10.1016/j.jpain.2017.03.008.

Shamay-Tsoory, S. G., & Mendelsohn, A. (2019). Real-life neuroscience: An ecological approach to brain and behavior research. *Perspectives on Psychological Science*. https://doi.org/10.1177/1745691619856350.

Shapiro, K., & Hillstrom, A. P. (2002). Control of visuotemporal attention by inferior parietal and superior temporal cortex. *Current Biology*. https://doi.org/10.1016/S0960-9822(02)01040-0.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. J., & Frith, C. D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science*. https://doi.org/10.1126/science.1093535.

Suvilehto, J. T., Glerean, E., Dunbar, R. I. M., Hari, R., & Nummenmaa, L. (2015). Topography of social touching depends on emotional bonds between humans. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1519231112.

Telzer, E. H., Masten, C. L., Berkman, E. T., Lieberman, M. D., & Fuligni, A. J. (2010). Gaining while giving: An fMRI study of the rewards of family assistance among white and latino youth. *Social Neuroscience*. https://doi.org/10.1080/17470911003687913.

Telzer, E. H., Masten, C. L., Berkman, E. T., Lieberman, M. D., & Fuligni, A. J. (2011). Neural regions associated with self control and mentalizing are recruited during prosocial behaviors towards the family. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2011.06.013.

Tölle, T. R., Kaufmann, T., Siessmeier, T., Lautenbacher, S., Berthele, A., Munz, F., et al. (1999). Region-specific encoding of sensory and affective components of pain in the human brain: A positron emission tomography correlation analysis. *Annals of Neurology*. https://doi.org/10.1002/1531-8249(199901)45:1<40::AID-ART8>3.0.CO;2-L.

Treede, R. D., Kenshalo, D. R., Gracely, R. H., & Jones, A. K. P. (1999). The cortical representation of pain. *Pain*. https://doi.org/10.1016/S0304-3959(98)00184-5.

Von Mohr, M., Kirsch, L. P., & Fotopoulou, A. (2017). The soothing function of touch: Affective touch reduces feelings of social exclusion. *Scientific Reports*. https://doi.org/10.1038/s41598-017-13355-7.

Woo, C. W., Roy, M., Buhle, J. T., & Wager, T. D. (2015). Distinct brain systems mediate the effects of nociceptive input and self-regulation on pain. *PLoS Biology*. https://doi.org/10.1371/journal.pbio.1002036.

Younger, J., Aron, A., Parke, S., Chatterjee, N., & Mackey, S. (2010). Viewing pictures of a romantic partner reduces experimental pain: Involvement of neural reward systems. *PLoS One*. https://doi.org/10.1371/journal.pone.0013309.