Brain mechanisms of social touch-induced analgesia in females

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Abstract
Supportive touch has remarkable benefits in childbirth and during painful medical procedures. But does social touch influence pain neurophysiology, i.e., the brain processes linked to nociception and primary pain experience? What other brain processes beyond primary pain systems mediate their analgesic effects? In this study, women (N = 30) experienced thermal pain while holding their romantic partner’s hand or an inert device. Social touch reduced pain and attenuated functional magnetic resonance imaging activity in the Neurologic Pain Signature (NPS)—a multivariate brain pattern sensitive and specific to somatic pain—and increased connectivity between the NPS and both somatosensory and “default mode” regions. Brain correlates of touch-induced analgesia included reduced pain-related activation in (1) regions targeted by primary nociceptive afferents (e.g., posterior insula, and anterior cingulate cortex); and (b) regions associated with affective value (orbitofrontal cortex), meaning (ventromedial prefrontal cortex [PFC]), and attentional regulation (dorsolateral PFC). Activation reductions during handholding (vs holding a rubber device) significantly mediated reductions in pain intensity and unpleasantness; greater pain reductions during handholding correlated with greater increases in emotional comfort, which correlated with higher perceived relationship quality and (a trend toward) greater perceived closeness with the romantic partner. The strongest mediators of analgesia were activity reductions in a brain circuit traditionally associated with stress and defensive behavior in mammals, including ventromedial and dorsomedial PFC, rostral anterior cingulate cortex, amygdala/hippocampus, hypothalamus, and periaqueductal gray matter. Social touch affects core brain processes that contribute to pain and pain-related affective distress in females, and should be considered alongside other treatments in medical and caregiving contexts.

Keywords: IMRI, Pain, Touch, Supportive touch, Handholding, Partner, Romantic partner, Stress, Analgesia, Social support

1. Introduction

Touch is an exquisitely social sense, capable of allowing accurate communication of specific emotional states. Interpersonal touch is associated with wellbeing, promoting pleasant feelings, approach-related behaviors, and reductions in aversive feelings and acute pain. Furthermore, touch is necessary for healthy development across mammals, and skin-to-skin contact early in life promotes healthy physical and psychological development.

The importance of supportive touch, i.e., interpersonal touch with an intention of providing emotional support, extends through life, particularly during stressful, painful, and threatening situations. Recent studies have shown that holding hands with one’s romantic partner provides greater pain relief than a variety of other conditions. The benefits of supportive touch extend to intense pain in real-life situations. In adolescents, holding hands with one’s mother can be particularly effective for coping with cancer treatment pain and disease pain, and during childbirth, a doula’s touch-related support can substantially reduce labor-related pain and duration, perinatal problems, and use of medication.

A seminal study by Coan et al. showed that handholding with a spouse reduced anticipatory anxiety during threat of shock paralleled by changes in brain activity in regions involved in affective meaning, value, and affect regulation. Responses to painful events were not tested. Studies by other groups showed that observing pictures of one’s romantic partner reduced experimentally evoked pain and elicited brain activity increases in affective meaning and regulation circuits.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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relieves pain primarily through influences on systems related to pain evaluation, emotional responses, and stress-related responses during pain.

In this functional magnetic resonance imaging (fMRI) study, we assess, for the first time, social touch effects on brain responses to pain (as opposed to pain anticipation) in females. We hypothesized that handholding will evoke analgesia by (1) directly targeting pain-specific processing measured using a previously validated neural marker for evoked pain\textsuperscript{175,26}; (2) modulating affective/cognitive-evaluative systems traditionally mediating stress and primary defensive behavior in mammals\textsuperscript{66,67,112,138,141,167,168} (in line with previous social touch effects\textsuperscript{26,29,43,171}); and (3) engaging somatosensory regions of the held hand (see Ref. 60), which may interfere with central nociceptive-specific processes\textsuperscript{12} measured using time-series functional connectivity.

2. Materials and methods

2.1. Participants

The study included 30 healthy women (mean age of 24.50 ± 6.65 years) with no history of psychiatric, neurological, or pain disorders and no current pain symptoms, who were in a committed and monogamous romantic relationship for at least 3 months (as previously reported\textsuperscript{99,100}). All participants and their male partners provided written informed consent that was approved by the institutional review board of the University of Colorado Boulder and were paid for their participation. All participants were able to complete the fMRI task and were considered appropriate for inclusion in the final analysis. The time frame of data collection for this study was October 2012 to June 2013.

2.2. Procedures

All participants and romantic partners first underwent a short pain calibration session to assure normal pain sensitivity, and familiarize them with the heat pain stimulation and computerized visual analogue scales (VAS) to be used during the scanner session.\textsuperscript{129} We also performed the calibration session in the male partners because they would receive pain at a later time as part of a different task (previously reported in Ref. 99). When using this VAS, participants were explicitly instructed to rate zero for warm sensations, even intense warm sensations, if they were not perceived as painful. This has been the standard procedure in our previous work\textsuperscript{75,76,99,100} and it is considered normative.\textsuperscript{129} It is not advised to use scales that mix nonpainful and painful sensations. Following Price and others,\textsuperscript{33,69,75,76,126–130} we adopted a maximum tolerable pain rating in the context of the experiment of 70 out of 100. The scale was anchored so that 100 was “the worst imaginable pain” (eg, third-degree burns over the whole body). As in previous studies,\textsuperscript{75,76,99,100} we ensured people did not show ceiling effects on ratings and had room to move up. Using this VAS, a rating of 40 is typically rated verbally as clearly painful in the moderate to strong pain range.\textsuperscript{33,69} During the calibration session, we ensured that the stimulus we used (47˚C, 11-second stimuli, 7.5-second plateau temperature) was within the tolerable range, yet reliably rated as painful for all subjects. All 47˚C stimuli presented during the calibration procedure (a total of 4 interspersed with other stimuli ranging from 45˚C to 49˚C, in random order) had to be rated above 20 using the VAS. The 47˚C stimulus was originally chosen on the basis of previous data\textsuperscript{75,166} indicating clear yet tolerable pain for the majority of subjects, and also on the basis of other studies showing that the threshold for specific nociceptors is ~45˚C\textsuperscript{91} and that human pain perception thresholds are in the range of 45 to 46˚C.\textsuperscript{130}

During the main fMRI session, we assessed brain and behavioral responses during 2 experimental conditions of interest (“baseline” condition [a] and “handholding” condition [b]), following an a-b-b-a experimental design (Fig. 1). During runs 1 and 4 (baseline condition), participants were holding an inert rubber device while experiencing painful stimulations (without the company of their romantic partners). The rubber device had an oval shape, and participants were told to hold the device and the partner’s hand in the same way (Fig. 1), applying a similar, comfortable amount of pressure. The rubber material had medium-hard consistency, and the temperature of the device was quickly adjusted to the temperature of the female participant’s hand. During runs 2 and 3 (for the entire duration of the runs), participants were holding hands with their romantic partner. Female participants could not see their partners nor their partners’ hand due to their relative position during scanning; however, they felt their partner’s hand for the entirety of the handholding run. In addition, before the start of each handholding run, the male partner was instructed to say a few words to the female partner so that she would know who she was holding hands with. All male partners said a few supportive words to their female partners right before the run started. Figure 1 provides a complete representation of this task structure and setting. The study was designed such that both conditions (handholding and baseline) consisted of 8 heat pain trials each (47˚C, 11-second stimuli, 7.5-second plateau temperature) distributed into 2 runs per condition (4 trials per run); therefore, the number of painful stimulations and the temperature were identical for both conditions, and the only difference relied on whether participants were holding hands with their romantic partners or not. Eight trials per condition has been shown to be sufficient to detect robust pain-related brain activation differences in previous work\textsuperscript{89,95,99–104,133,156,166,176} Heat painful stimulations were administered to the volar surface of the participants’ left forearm using a magnetic resonance imaging–compatible PATHWAY ATS (Advance Thermal Stimulation) thermode with 16-mm diameter (Medoc, Ltd., Ramat Yishai, Israel). The thermode was moved in a random manner to a different (premarked) location in the volar forearm after each run. After each pain stimulus (trial), participants rated, using a computerized visual analogue scale (VAS), pain intensity (“how intense was the painful stimulus?,” ranging from 0, “not intense at all” to 100, “the most intense imaginable”) and pain unpleasantness (“how unpleasant was the painful stimulus?,” ie, how much did the stimulus “bother” you?, from 0, “not at all unpleasant” to 100, “the most unpleasant imaginable”). At the end of each run, we collected run-level measures of emotional comfort (“How much emotional comfort have you felt?” from 0, “no emotional comfort at all” to 100, “the most emotional comfort imaginable”), using a computerized VAS.

Furthermore, although we do not use these measures in the current study, we collected measures of perceived closeness with the romantic partner and emotional empathic tendency as reported in our previous studies on separate experimental tasks of this study (c.f., Refs. 99 and 100).

2.3. Experimental design and statistical analysis of behavioral data

We used a within-subjects a-b-b-a design. Each condition consisted of 8 trials divided into 2 runs per condition (4 trials
handholding (vs baseline) and greater perceived quality of the romantic relationship (assessed 2 weeks before scanning during the calibration session). Summary statistics for these results are provided in the main text.

2.4. Analyses of functional magnetic resonance imaging data

2.4.1. Magnetic resonance imaging acquisition and preprocessing

Functional brain activity was measured using a Siemens TrioTim 3T scanner, covering the brain in 26 interleaved transversal slices (3.4 mm isomorphic voxels), with a T2* weighted EPI GRAPPA sequence (time of repetition [TR] = 1.3 seconds, echo time [TE] = 25 ms, flip angle = 50°, field of view [FOV] = 220 mm). SPM8 was used for preprocessing for functional images, using a standard pipeline for motion correction, slice-time correction, spatial normalization to Montreal Neurological Institute space, and spatial smoothing of images using an 8-mm FWHM Gaussian kernel. For spatial normalization, T1 structural MPRAGE images (1-mm isomorphic voxels) were first co-registered to the mean functional image and then normalized to the SPM template using unified segmentation. Preprocessed functional images were resampled at a voxel size of 2 x 2 x 2 mm. Regarding motion correction, translation and rotation estimates (x, y, z) were less than 2 mm or 2°, respectively, for all the participants.

2.4.2. First-level single-subject functional magnetic resonance imaging analyses

We used a general linear model analysis approach as implemented in SPM8 software to estimate, for each subject, brain responses to pain during (1) single trials for the baseline and handholding conditions to be used in the whole-brain multilevel mediation model and (2) an average brain response to pain (first half and second half of painful stimulus duration), pain anticipation, and pain ratings during the baseline and handholding conditions to be used to compute Neurologic Pain Signature (NPS) responses for each subject and condition. Modeling the data considering the 2 halves of painful stimulation separately provides greater temporal resolution by allowing effects to be examined early and late in the stimulus epoch (please see Refs. 42 and 156). We chose our approach because (1) we were interested in studying NPS effects on both phases of the pain experience for 2 reasons: (a) we had repeatedly observed that placebo analgesia exerted stronger effects in later (as opposed to earlier) phases of the pain trial and also (b) to ensure that all events (ie, pain anticipation, early and late phases of the pain experience, and pain ratings) had the same duration, making these events comparable in terms of NPS response; and (2) previous studies have traditionally identified significant, clinically and behaviorally relevant information contained within the temporal domain of brain responses to pain (see Refs. 42, 102, 131, and 156), and we were interested in pursuing a more temporally detailed analysis of handholding effects on pain. We also ran first-level models using a single regressor to estimate brain responses to the entire pain period and we report those results in the supplementary information (available online at http://links.lww.com/PAIN/A792).

For both baseline and handholding conditions, either single-trial pain regressors or a regressor modeling all pain trials for each condition was created, by convolving each painful stimulation trial pain regressors or a regressor modeling all pain trials for each condition was created, by convolving each painful stimulation...
period with a canonical hemodynamic response function. The model also included regressors modeling the anticipatory periods and the rating periods. The remaining “rest” period served as an implicit baseline. Finally, the model included 24 motion regressors (3 translation and 3 rotation regressors, plus their first and second derivatives). Parameter estimates were calculated at each voxel using the general linear model. A high-pass filter was used to remove low-frequency signal fluctuations (1/180 Hz). We calculated single-trial pain contrast images for each participant, for the 8 baseline and 8 handholding (vs implicit baseline) trials. The individual contrast images were carried forward to a whole-brain multilevel mediation model computed using publicly available software (https://github.com/cantlab/MediationToolbox).

2.4.3. Signature responses

For each female participant, we computed a single scalar value representing their expression of the NPS pattern for the baseline and handholding contrast images (as explained in detail in previous articles100,104 for the pain, anticipatory, and pain rating periods. The NPS includes voxel weights in an a priori defined mask of brain regions that were significantly related to the term “pain” in the Neurosynth meta-analytic database (http://neurosynth.org/, see Ref.155 for a detailed description). Thus, voxel weights outside this mask did not contribute to the pattern expression value. For every contrast image of each female participant (baseline and handholding, for the periods of interest, ie, first-half pain, second-half pain, anticipation, and pain ratings), we computed the cross product of the vectorized activation contrast image ($\beta_{\text{NPS}}$) with the NPS pattern of voxel weights ($\text{NPS} \cdot \omega_{\text{NPS}}$), ie, $\beta_{\text{NPS}} \cdot \text{NPS} \cdot \omega_{\text{NPS}}$, yielding a continuous scalar value for each person and condition (baseline and handholding).

2.4.4. Multilevel whole-brain mediation analyses

First-level contrast images for the single-trial first pain period regressors for each subject were carried forward to a multilevel mediation analysis model. To avoid that single-trial estimates could be driven by movement artifacts or other sources of noise, trial estimates with variance inflation factor of 5 or more were excluded from further analysis.86,100 We then tested relations between Condition (handholding vs baseline), single-trial trials and handholding contrast images (as explained in detail in previous articles100,104 for the pain, anticipatory, and pain rating periods. The remaining “rest” period served as an implicit baseline. Finally, the model included 24 motion regressors (3 translation and 3 rotation regressors, plus their first and second derivatives). Parameter estimates were calculated at each voxel using the general linear model. A high-pass filter was used to remove low-frequency signal fluctuations (1/180 Hz). We calculated single-trial pain contrast images for each participant, for the 8 baseline and 8 handholding (vs implicit baseline) trials. The individual contrast images were carried forward to a whole-brain multilevel mediation model computed using publicly available software (https://github.com/cantlab/MediationToolbox).

In this study, we were specifically interested in path a, showing activation reductions during handholding (vs baseline), and path $a \times b$ of significant brain mediators of the effect of handholding on reducing pain unpleasantness. Resulting activation maps were thresholded at $q < 0.05$ false discovery rate (FDR)-corrected within an extensive whole-brain gray-matter mask including 352,328 voxels (corresponding to a voxel threshold of $P = 0.001$) and across mediation paths.9,86,100 To facilitate interpretation of the functional maps, adjacent voxels were displayed at thresholds of $P = 0.005$ and $P = 0.01$ uncorrected.

2.4.5. Assessing overlap between brain effects of handholding during pain and previously identified brain mechanisms of distraction

An important question is how similar handholding effects are to other manipulations of cognitive demand and attentional diversion (“distraction”). This study did not compare handholding with other strategies, but it is possible to compare the mediation maps we identified to known patterns from other studies, to assess how similar handholding is to tasks that involve manipulation of cognitive demand. For the handholding effects (path a, handholding vs baseline—rubber device—on brain activity during pain) and the mediation effect maps (a $\times b$ for intensity and unpleasantness), we calculated the similarity with each of the 7 major cortical networks in Yeo et al.170 We used a Dice coefficient40 metric normalized across networks to reflect the percentage of significant voxels in each map (FDR $q < 0.05$) that fell within each network. We compared this with 2 meta-analyses of working memory, a widely studied cognitively demanding task that has shown some of the strongest “distraction” effects on pain.18,19 Furthermore, to estimate the overall similarity between handholding and working memory across cortical networks, we calculated the correlation matrix across normalized Dice coefficients for all images.

2.4.6. Neurologic pain signature-to-whole-brain time-series functional connectivity analysis

A time-series connectivity analysis was performed to assess the regions that were more strongly/weakly connected (functionally correlated) with the pain-specific NPS marker during handholding vs baseline runs. This is similar to a psychophysiological interaction analysis120 but is focused on changes related to sustained affective state across the entire run, and uses the NPS response (moment-by-moment, ie, NPS response volume-by-volume time series regressor) as a “pattern of interest” rather than a single region.8 We used a general linear model analysis approach as implemented in SPM8 software to estimate, for each subject, the pattern of time-series connectivity with a regressor representing NPS response moment-by-moment convolved with a canonical hemodynamic response function. The model also included 24 motion regressors (3 translation and 3 rotation regressors, plus their first and second derivatives). Parameter estimates were calculated at each voxel using the general linear model. A high-pass filter was used to remove low-frequency signal fluctuations (1/180 Hz). A contrast image of interest was generated for each subject for the NPS-regressor of interest. Contrast images were then carried forward to a second-level random-effects group analysis in SPM8. We restricted our analysis to voxels outside the NPS (the NPS covers approximately 12% of the brain150). Results were corrected for multiple comparisons $q < 0.05$ FDR within a whole-brain mask excluding NPS voxels.
3. Results

3.1. Handholding reduces pain intensity and unpleasantness and increases emotional comfort

Handholding, relative to holding a rubber squeeze ball, significantly reduced reports of pain intensity (t = 2.17, P = 0.038 [N = 30]) and unpleasantness (t = 4.82, P = 0.00004 [N = 30] (Fig. 1). In parallel, it increased emotional comfort (t = 3.65, P = 0.001). Greater increases in emotional comfort during handholding predicted greater reductions in pain intensity (r = 0.41, P = 0.024 [N = 30]) and unpleasantness (r = 0.48, P = 0.007 [N = 30]). Moreover, greater increases in emotional comfort during handholding were associated with higher perceived relationship quality (Sternberg Triangular Love Scale, STLS, r = 0.44, P = 0.016 [N = 30]) (Fig. 1) and a trend (significant one-tailed) toward higher perceived closeness with the romantic partner (the Inclusion of Other into the Self, IOS, r = 0.345, P = 0.085 [N = 26]; we lost 4 subjects’ data due to a software error). Of note, all participants reported high quality of the romantic relationship (mean score on the STLS [std] = 390.5 [25.4], in a scale ranging from 45 to 415), between 316 and 413, thus reflecting a range from “somewhat above average” to “significantly above average.”

No dyads reported low relationship quality, which limits our possibility to investigate dyadic differences in relationship quality in more detail. For the closeness measure, the IOS scale, measuring how close the respondent feels with another person, we found a mean (std) score of 5.50 (1.08), in a scale ranging from 1 to 7, which corresponds to the range from “strong overlap” to “very strong overlap.”

3.2. Handholding effects on acute brain responses to pain

3.2.1. Handholding reduces Neurologic Pain Signature responses during pain

We divided the painful period into early and late phases (5.5 seconds each) to study handholding effects on both phases. Previous work on placebo effects has shown stronger placebo effects later rather than earlier in the trial.42,156 This approach also ensured that pain anticipation, experience (early and late), and pain reporting events were all comparable in duration, facilitating comparisons of NPS responses across all these events.

Figure 2 shows the NPS, a map of voxel weights predicting increased (yellow) and decreased (blue) pain given activity in each voxel (see also Supplementary Fig. 1 for a more extensive visualization of heat-evoked brain responses in this task, available online at http://links.lww.com/PAIN/A792). Applying the NPS weights reduces a brain image into a single number, the NPS response, which reflects activity in this pain-linked brain system. Figure 2 shows responses to all events (anticipation, early and late heat pain, and pain ratings) and a representation of the trial structure.

As expected, the NPS responded strongly during early and late pain (early: control condition: t = 11.57, effect size Cohen’s d = 2.11; handholding: t = 11.47, d = 2.09, P-values <0.00005; late: control condition: t = 13.74, d = 2.5; handholding: t = 14.38, d = 2.62, P-values <0.00005). The NPS did not respond during pain anticipation (control condition: t = 1.59, P = 0.12; handholding: t = 0.93, P = 0.36) or rating periods (control condition: t = 0.84, P = 0.41; handholding: t = −0.86, P = 0.40) (Fig. 2). These findings support the sensitivity and specificity of the NPS for pain, in line with more extensive validations published previously176 (for review, see Refs. 87 and 164).

Importantly, handholding significantly reduced NPS responses during both early and late pain (early: t = 2.10, effect size d = 0.38, P = 0.04; late: t = 2.04, d = 0.37, P = 0.05). Neurologic Pain Signature reductions during acute pain did not correlate with reductions in pain intensity (P = 0.55) nor unpleasantness (P = 0.83). This effect of handholding significantly reducing NPS response is interesting in light of recent evidence showing that the NPS is unaffected by placebo treatment,176 cognitive reappraisal,160 reward,12 knowledge about drug-delivery context,156,176 or perceived control.16 For example, the effect size of handholding here (d = 0.38) was considerably larger than the average effect of placebo (d = 0.07) across 20 studies.176 Although responses in the NPS were reduced by handholding, the sizes of the effects of handholding (path a) and correlation with pain (path b) were not large enough for the joint a x b mediation test to be significant. Thus, we conclude that there are other important pathways involved. The whole-brain mediation analysis (reported below) supplemented the NPS test, and revealed additional brain regions that are significant mediators.
3.2.2. Handholding increases time-series connectivity between Neurologic Pain Signature, primary somatosensory, and default mode network regions

A time-series connectivity analysis was performed to assess the regions that were more strongly/weakly connected (functionally correlated) with the pain-specific NPS marker during handholding vs baseline runs. This is similar to a psychophysiological interaction analysis but is focused on changes related to sustained affective state across the entire run, and uses the NPS response as a “pattern of interest” rather than a single region. We restricted our analysis to brain voxels outside the NPS (the NPS covers approximately 12% of the brain).

Handholding significantly increased time-series correlations (across the entire run) between NPS responses and “default mode” network regions including medial prefrontal cortex (PFC), posterior cingulate cortex (PCC) and precuneus, temporoparietal junction (TPJ), as well as the ventral striatum (accumbens) and middle temporal gyrus (Supplementary Table 1, available online at http://links.lww.com/PAIN/A792; and Fig. 3). Handholding also increased NPS connectivity with the right primary somatosensory cortex (SI) contralateral to the hand being held by the romantic partner (left hand. Supplementary Table 1, available online at http://links.lww.com/PAIN/A792; Fig. 3). Increases in connectivity between NPS and SI during handholding were significantly associated with greater pain unpleasantness relief across individuals \( r = 0.382, P = 0.037 \); the same trend was observed for pain intensity \( r = 0.312, P = 0.094 \). Connectivity changes between NPS and other regions showing NPS connectivity changes during handholding (including PCC, MPFC, TPJ, and accumbens) did not show significant correlations with pain relief in this sample (all \( P > 0.2 \)) but may still be important for reevaluating pain. There were no significant decreases in NPS–brain time-series correlations during handholding. The results suggest that NPS responses are significantly more integrated with other systems, particularly the “default mode” network (DMN) and SI regions of the held hand, during handholding, and that increased integration with primary sensory representations of the hand receiving supportive care is correlated with analgesic effects.

In sum, these findings demonstrate moderate reductions in the NPS—a validated, pain-linked and (in tests to date) pain-specific measure—and enhanced connectivity between the NPS and both default-mode and somatosensory systems.

3.2.3. Pain-evoked brain activation reductions mediating reductions in pain intensity and unpleasantness during handholding

Although the NPS findings demonstrate reductions in pain-related systems, they also indicate that NPS reductions are unlikely to fully explain the effects of handholding on pain. In addition, recent research clearly indicates that other systems are involved in constructing pain experience. To identify the brain systems that most strongly mediate handholding effects on pain reduction, we ran whole-brain multilevel mediation analyses across trial-by-trial estimates of brain and behavioral responses during pain. The inferior panel of Figure 4 shows a diagram of the mediation model, in which X indicates the experimental condition (handholding vs baseline), Y indicates pain unpleasantness (and intensity in a separate model) ratings for each trial, and M indicates brain activation maps for early pain across individual trials (beta images from single-trial analysis). In the mediation analysis framework, path a models the effect of handholding vs baseline on pain-evoked brain responses. Path b is the relationship between brain activity during pain and pain reports across single trials, within person. The product a × b is a map of mediators jointly linked to both handholding and pain reports.

The results for path a (handholding vs baseline) show that handholding significantly reduced pain-evoked activation in brain regions traditionally associated with pain processing and regulation (secondary somatosensory cortex and posterior insula, mid/anterior insula, dorsal anterior cingulate cortex [ACC], dorsal and ventral lateral PFC, thalamus, dorsal caudate, periaqueductal gray matter [PAG], amygdala, and cerebellum; Figure 4). Handholding also reduced pain-evoked responses in brain regions more broadly involved in value, reward/punishment processes, generation of affective meaning, and perspective taking (orbitofrontal cortex [OFC], dorsomedial prefrontal cortex [DMPFC], superior temporal gyrus, and temporal pole) (\( q < 0.05 \) FDR-corrected, gray-matter mask) (Supplementary Table 2, Supplementary Figure 2, available online at http://links.lww.com/PAIN/A792; Fig. 4).

![Figure 3](http://links.lww.com/PAIN/A792)  
**Figure 3.** Neurologic pain signature connectivity during handholding (vs baseline). Brain regions showing significantly greater time-series correlation with the NPS (Neurologic Pain Signature) during handholding (vs baseline) runs. The red circle represents the location of a 6-mm diameter sphere that was placed in the peak coordinate of SI from which average individual beta image values were extracted (for each subject) to compute correlations between SI–NPS functional connectivity estimations and pain intensity and unpleasantness reductions during handholding (across subjects). The correlation plot illustrates a significant positive relationship between SI–NPS connectivity increases during handholding and reductions in pain unpleasantness (see main text for summary statistics).
The results for path a for the intensity model showed that the strongest brain mediators of handholding effects on pain intensity included regions that are activated during pain, ie, the dorsal/rostral ACC, anterior insula, right dorsolateral and ventrolateral prefrontal cortices (DLPFC and VLPFC), and amygdala, and regions that are not significantly activated in response to pain, such as the superior parietal, DMPFC/VMPFC, OFC, and middle/inferior temporal gyrus (Supplementary Table 3, Supplementary Figure 2, available online at http://links.lww.com/PAIN/A792; Fig. 4). (B) Brain mediators of handholding effects on pain intensity, ie, greater pain-evoked brain activation reductions in these regions predict greater pain intensity reductions during handholding (see also Supplementary Table 3, http://links.lww.com/PAIN/A792). (C) Brain mediators of handholding effects on pain unpleasantness, ie, greater pain-evoked brain activation reductions in these regions predict greater pain unpleasantness reductions during handholding (see also Supplementary Table 4, http://links.lww.com/PAIN/A792). ACC, anterior cingulate cortex; PAG, periaqueductal gray matter.

Figure 4. Whole-brain multilevel mediation results. (A) Illustration of path a effects, ie, effects of condition (handholding vs baseline) on brain responses to pain. Brain image maps display significant (q < 0.05 FDR-corrected, gray-matter mask) brain activation reductions in regions including the dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (VMPFC), anterior cingulate cortex (ACC) medial prefrontal cortex, orbitofrontal cortex (OFC) thalamus, secondary somatosensory cortex, amygdala, periaqueductal gray matter (PAG) temporal cortices, and cerebellum. (B) Brain mediators of handholding effects on pain intensity, ie, greater pain-evoked brain activation reductions in these regions predict greater pain intensity reductions during handholding (see also Supplementary Table 3, http://links.lww.com/PAIN/A792). (C) Brain mediators of handholding effects on pain unpleasantness, ie, greater pain-evoked brain activation reductions in these regions predict greater pain unpleasantness reductions during handholding (see also Supplementary Table 4, http://links.lww.com/PAIN/A792). ACC, anterior cingulate cortex; PAG, periaqueductal gray matter.

The results for path a × b for the intensity model showed that the strongest brain mediators of handholding effects on pain intensity included regions that are activated during pain, ie, the dorsal/rostral ACC, anterior insula, right dorsolateral and ventrolateral prefrontal cortices (DLPFC and VLPFC), and amygdala, and regions that are not significantly activated in response to pain, such as the superior parietal, DMPFC/VMPFC, OFC, and middle/inferior temporal gyrus (Supplementary Table 3, Supplementary Figure 2, available online at http://links.lww.com/PAIN/A792; Fig. 4).

Significant mediators of pain unpleasantness (path a × b, unpleasantness model) partially overlapped with mediators of pain intensity, and included rostral/dorsal ACC/supplementary motor area regions, subgenual ACC, DLPFC, VLPFC and VMPFC, OFC, ventral anterior insula, and middle temporal gyrus (Supplementary Table 4, Supplementary Figure 2, available online at http://links.lww.com/PAIN/A792; Fig. 4). All regions showed a positive mediation effect indicating that significant decreases in pain-evoked activation during handholding were associated with decreases in pain ratings during handholding. There were no regions showing the opposite effect.

In summary, holding hands with a close romantic partner during pain exerts several protective brain and behavioral effects (Fig. 5): (1) handholding has analgesic properties that are associated with increases in emotional comfort provided by the partner’s support, which is associated with higher quality of the romantic relationship; (2) congruently, handholding attenuates pain-specific processing as identified using the previously validated NPS brain measure; (3) handholding increases the time-series correlation (functional connectivity) between the NPS and the DMN, which has been traditionally associated with processing “inner state” status, “self” and “other” related content, as well as regions of the TPJ, and temporal gyri, previously associated with “social,” “empathy,” and “perspective taking” related processes; (4) handholding increases the time-series correlation between the NPS and SI contralateral to the hand held by the romantic partner, which has been directly involved in processing pleasant affective touch60 and in corticocortical
3.2.4. Overlap between brain effects of handholding and brain effects of distraction (using a working memory task)

In each handholding mediation map (path a, path a × b for intensity, and path a × b for unpleasantness), over 50% of the significant voxels fell within the DMN or limbic network. There was also overlap with the frontoparietal network (~30%) and ventral attention network (~10%). These are shown in the polar plots in Supplementary Figure 3, and values are in Supplementary Table 5 (available online at http://links.lww.com/PAIN/A792). We compared this with 2 meta-analyses of working memory, a widely studied cognitively demanding task that has shown some of the strongest “distraction” effects on pain.16,19 For both157,160 Wager and Smith’s working memory meta-analysis and the Neurosynth “reverse inference” map for the term working memory, significant voxels were concentrated in the frontoparietal network (~30%-50%) and dorsal attention network (~25%-35%), with some overlap with ventral attention network (~10%) (Supplementary Fig. 3 and Supplementary Table 5, available online at http://links.lww.com/PAIN/A792). Furthermore, to estimate the overall similarity between handholding and working memory across cortical networks, we calculated the correlation matrix across normalized Dice coefficients for all images (Supplementary Fig. 3, available online at http://links.lww.com/PAIN/A792). The handholding maps were similar with one another (r = 0.71-0.96), and the 2 working memory maps were similar (r = 0.94), but the handholding and working memory maps shared little overlap (r = 0.22-0.44).

4. Discussion

This study is the first to show (1) social touch effects on brain responses to pain (as opposed to pain anticipation27,29); (2) social touch effects on a validated measure that tracks pain specifically (NPS155) and not other affective events; and (3) potential mechanisms of how social touch reduces pain intensity and unpleasantness through mediation and connectivity analyses. This study provides evidence showing that handholding affects pain in fundamental ways by directly reducing central nociception and stress-related brain responses during pain in females. Many interventions have been studied behaviorally including pharmaceutical, social, and placebo interventions, and many have significant effects in reducing pain. However, the brain mechanisms through which they exert its protective effects are likely to be different. We show, for example, one differential mechanism between placebo and handholding in mediating analgesia, because handholding involved reductions in NPS pain-specific (nociceptive) processing, whereas placebo analgesia has been
systematically observed to not cause NPS reductions.\textsuperscript{176} Identifying these mechanisms is a first step toward understanding when and in whom each of these interventions may work best.

We interpret handholding as an analgesic intervention based on social support. It is well known (reviewed in Gallace and Spence, 2010) that social touch communicates emotion and intention. Handholding has previously been considered a supportive social behavior\textsuperscript{22,29,51,58} because it is a common natural form of expressing support and affection in times of struggle, pain, and suffering\textsuperscript{61,62,143,145,148,159} and has been associated with reconciliation and soothing behaviors.\textsuperscript{153} Furthermore, handholding reduces autonomic arousal and reports of anxiety.\textsuperscript{29} Importantly, holding hands with the romantic partner increases connectivity of the pain pattern (NPS) with regions involved in self/other processing (DMN and TPJ) and somatosensory processing of the hand that is being held (SI). Increased connectivity between NPS and SI for the held hand is associated with reductions in pain unpleasantness. This finding suggests modulation of pain by self/other representations engaged in DMN and TPJ, which may be activated by processing social touch input in SI of the held hand. Furthermore, handholding reduces pain-evoked activations (path a) in regions overlapping with a stress response circuit in mammals that includes the ventromedial PFC/subgenual cingulate, hypothalamus, amygdala/hippocampus, and PAG.\textsuperscript{7,65,72,112,138,141,167,168} Some of these regions are also significant mediators of pain intensity and unpleasantness reductions during handholding. This may suggest that attenuation of stress-related brain responses specifically during pain is critical in reducing the subjective pain experience through social touch. This interpretation aligns with the reported increases in emotional comfort experienced during handholding, which correlated with reductions in pain and were predicted by higher quality of the romantic relationship and higher perceived closeness with the romantic partner.

Several interesting potential mechanisms may contribute to the present findings (and are not necessarily mutually exclusive). First, the analgesic effects of supportive touch may reflect an attentional shift toward human touch and therefore provide a distraction from pain. Second, this effect could reflect the positive consequences of sharing the heaviness of a painful experience with another person,\textsuperscript{100} thus leading to changes in appraisal and affective meaning of the pain experience. Third, handholding with the romantic partner may provide a positive stimulus that counteracts negative affect and pain.\textsuperscript{93} We indeed observed significant increases in emotional comfort, which were correlated with the magnitude of analgesic effects. The analgesic findings and brain mechanisms observed here may also be related to general touch-evoked pleasantness.\textsuperscript{47,69,110} Also, although our study shows some parallels with studies investigating the effects of observing pictures of the romantic partner while receiving pain,\textsuperscript{108,171} we do not know to which degree these interventions involve very similar mechanisms or have the same impact on pain processing, because they have never been directly compared.

4.1. Handholding reduces nociceptive-specific (neurologic pain signature) brain responses during pain

The NPS\textsuperscript{115} is an fMRI-based pattern of voxel weights indicating relative activity levels across different brain regions that, together, are predictive of thermal, mechanical, electrical, and visceral pain\textsuperscript{16,88,99,100,109,155} but no other emotionally unpleasant experiences including anticipatory threat cues, social rejection, pain in the romantic partner, or visually evoked unpleasant emotions and sensations without a bodily pain component.\textsuperscript{23,88,99,109,155} Therefore, the NPS is a highly specific brain measure for somatic pain that is well validated across studies. Our findings argue in favor of a reduction of central nociceptive-specific processing during handholding (effect size $d = 0.38$), specifically during pain (and not anticipation or pain rating periods). This differs from previous studies focusing on changes during anticipatory threat responses during handholding.\textsuperscript{24,29,78,105} Importantly, other pain regulation strategies such as placebo and cognitive self-regulation fail to downregulate this nociceptive-specific marker\textsuperscript{168,174} indicating that handholding vs other more purely cognitive strategies may at least partially differ in their mechanism of action.

4.2. Handholding increases neurologic pain signature–pattern connectivity to somatosensory regions of the held hand and self/other processing regions

Moment-by-moment expression of the NPS (a single measure reflecting brain nociceptive processing) was significantly more correlated with signal time course in SI of the held hand during handholding runs (vs baseline runs)—and this change in NPS–SI connectivity correlated with greater reductions in pain unpleasantness. Some studies have suggested that touch reduces pain and that, at least in some instances, a critical balance between nociceptive and touch-related processing at the brain level (with minimal contribution from peripheral and spinal cord levels) can drive pain perceptions.\textsuperscript{36,73,132} Our findings propose a role for SI in corticocortical inhibition of central nociception in the context of supportive social touch. It has been demonstrated that touch does not only provide discriminative input to the brain but also, and relevantly, affective input.\textsuperscript{111} Social and affective context can strongly influence touch pleasantness\textsuperscript{46,47,110,151} and brain processing of touch at sensory integration levels,\textsuperscript{45,47,82,115} particularly in SI.\textsuperscript{60} Gazzola et al.\textsuperscript{60} showed that SI can be either strongly activated or inhibited by touch, depending on the affective meaning of touch for the perceiver. In line with our study results, their findings indicate a substantial role of affective meaning in modulating touch-evoked brain responses.

Furthermore, handholding increases functional connectivity between the nociceptive process captured by the NPS marker and the DMN, particularly the PCC/precuneus region and medial PFC. This may indicate higher functional integration between nociceptive-specific processes and DMN function and contents. The DMN has been traditionally associated with self-related processing and mentalizing, spontaneous thought, thinking about others, empathic accuracy, and conceptual processes.\textsuperscript{4,5,90,60,76,114,146,175} In our study, regions directly involved in social cognition such as the temporal cortex and TPJ\textsuperscript{1,2,8,15,140,172,175} were significantly more functionally connected moment-by-moment to the NPS pattern during handholding. Together, these observations may suggest a shift in attention toward social- and self-oriented mentalizing during pain in the handholding condition, resonating with recent findings of increased brain-to-brain coupling between the 2 partners in this handholding-pain context.\textsuperscript{52}

4.3. Handholding hypoalgesic effects are related to attenuation of brain responses in a stress-related brain system during pain

Our mediation model (path a) showed that handholding strongly reduced responses in brain regions that receive direct nociceptive input and that are usually activated during pain,\textsuperscript{52,99–102,104,123,131,155} including the thalamus, secondary somatosensory cortex, insula, ACC, and PAG. This finding is in line with the observed reduction in
NPS responses, further reinforcing the idea that handholding directly influences brain nociceptive processing. Brain activation reductions during handholding included a region compatible with the hypothalamus, the amygdala/hippocampus complex, the PAG, and regions in the ventral prefrontal and OFC cortex. Furthermore, handholding related reductions in pain intensity and unpleasantness were mediated (path a × b) by brain activation reductions in VMpFC and VLPFC, subgenual and rostral ACC, ventral AIns, amygdala, and temporal regions. This functional anatomy is highly compatible with circuitry frequently involved in mediating defensive responses in stress contexts\textsuperscript{7,25,57,58,60}, therefore, our findings may indicate an effect of handholding on attenuating not only central nociceptive processing but also stress-related brain responses specifically during the painful procedure.

Prefrontal and OFC regions have been associated with cognitive regulation of emotion and pain, specifically in the context of placebo\textsuperscript{122,136} and cognitive reappraisal of negative emotions.\textsuperscript{17,41,117–119} Also, most of these prefrontal and OFC regions mediating reductions in pain intensity and unpleasantness are not usually activated by nociceptive stimulation\textsuperscript{4,123}, these regions have been involved in attention control and orientation, maintenance of relevant representations of stimuli, social/affective meaning, value, and reward properties associated with stimuli and situations.\textsuperscript{13,35,37,57–59,72,124,125,137} These regions, and not the NPS marker, directly mediate reductions of reported pain during handholding, suggesting that changes in cognitive/affective regulation circuits are critical for reductions of reported pain in this context, in line with previous studies.\textsuperscript{28,29,61,62}

In sum, we can conclude that (1) handholding is mediated by some of the voxels involved in the NPS, but the overlap with the NPS is too low for the overall NPS measure to be a mediator; and (2) other regions not involved in the NPS (e.g., OFC) were identified as mediators, pointing to additional pathways beyond the NPS in mediating social modulation of pain in females.

4.4. Limitations and conclusion

Our study is limited in that we did not have an extra control condition involving handholding with a stranger. Previous studies have shown that holding hands with a stranger (or viewing pictures of a stranger\textsuperscript{43}) did not evoke significant attenuation of pain.\textsuperscript{29,61} And although early studies suggested stranger handholding mildly attenuated responses to threat of shock,\textsuperscript{28,29} a recent replication involving a large representative sample revealed little or no stranger effect.\textsuperscript{27} This may suggest that the degree of closeness between the 2 people holding hands may play a critical role in the soothing and analgesic effects of handholding. Interestingly, greater partner’s empathy has been associated with greater analgesia and its physiological underpinnings.\textsuperscript{118,61–63} In concordance with these studies, our results indicate that greater handholding analgesia is associated with greater perceived emotional comfort during handholding, which is in turn predicted by greater perceived quality of the romantic relationship and greater perceived closeness with the romantic partner. This study is also limited in that it does not include other control conditions including touch by different humans vs different mechanical devices, and uncomfortable touch. Also, an important question is how similar the handholding effects are to other manipulations of cognitive demand and attentional diversion ("distraction"). This study did not compare handholding with other strategies, but it is possible to compare the maps we identified to known patterns from other studies to assess how similar handholding is to tasks that involve manipulation of cognitive demand. In our supplementary analyses, we found a clear distinction between handholding effects and cognitive demand effects on the brain. This does not preclude the presence of some shared processes, and more precise comparisons of handholding and distraction effects in the same participants, ideally with quantitatively matched effects on pain, should be done in future studies. Our results do, however, suggest the involvement of some qualitatively distinct brain systems between handholding and distraction. Finally, our findings are not necessarily generalizable to men. Sex has emerged as a critical variable in pain research and other health domains.\textsuperscript{3,9,46,64,90,94,113,156} Women are more susceptible to chronic pain disorders\textsuperscript{3,5,46,64,90,94,113,156} and mechanisms and treatment responses are demonstrably different in some cases.\textsuperscript{3,15,85,96} We tested only female participants here, and although a previous handholding study did not find moderation by sex,\textsuperscript{27} it remains possible that males will show different responses to and/or mechanisms of social touch. We focused on women as a first step because they are at greater risk of clinical, postoperative, and procedural pain\textsuperscript{54} and have shown stronger brain, psychological, and physiological responses to negative affective stimuli.\textsuperscript{148,161}

In conclusion, handholding elicits analgesia in females through a cascade of brain changes that transcend anticipatory threat modulation and directly target specific nociceptive processes and pain-evoked responses in stress-, emotion-, and attention-related circuits. The effects of handholding are not confined to modulating brain signal during pain exclusively. Instead, they alter the state of brain connectivity along the duration of the experimental procedure by significantly engaging self-other and somatosensory-related processes of the hand being held. Brain and behavioral findings in the current study indicate that handholding-elicited analgesia may be deeply modulated by social-affective nuances in the relationship between romantic partners.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A792.

Supplemental video content

Video content associated with this article can be found online at http://links.lww.com/PAIN/A793.

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