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Brain mechanisms of social touch-induced analgesia in females

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Running Head: Handholding effects on brain responses to pain

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ABSTRACT

Supportive touch can have 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? And 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 fMRI 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 (a) regions targeted by primary nociceptive afferents (e.g., posterior insula, and anterior cingulate cortex (ACC)); 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 ACC, amygdala/hippocampus, hypothalamus and PAG. Social touch affects core brain processes that contribute to pain and pain-related affective distress, and should be considered alongside other treatments in medical and caregiving contexts.

INTRODUCTION

Touch is an exquisitely social sense [47], capable of allowing accurate communication of specific emotional states [41,64,65]. Interpersonal touch is associated with wellbeing [47,53], promoting pleasant feelings, approach-related behaviors [45,46,90,109] and reductions in aversive feelings and acute pain [24,26,27,56,57,77,98,99,107]. Furthermore, touch is necessary for healthy development across mammals [47–50] and skin-to-skin contact early in life promotes healthy physical and psychological development [13,31,47,71,114,127,139,151], reducing reactivity to stress [46] and pain-related responses [13,23].

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 [56,57,102] 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 [150]; and during childbirth, a doula's touch-related support can substantially reduce labor-related pain and duration, perinatal problems and use of medication [19,28,74,78,135,137,140].

A seminal study by Coan and colleagues [27] 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 [40,162]. Other studies have indicated a relevant role for somatosensory regions [108] in encoding the affective significance of interpersonal touch [55,134] and touch-evoked pleasantness [44,55,104]. In spite of this progress, it is still unknown which brain regions mediate the effects of supportive touch on pain—i.e., which regions are jointly affected by touch interventions and directly linked with pain reductions. It is also unclear whether touch influences the pathways most strongly linked with the transmission of pain-related (nociceptive) information from the body and the genesis of pain, or rather relieves pain primarily via 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[25,27]). We hypothesized that handholding will evoke analgesia by (i) directly targeting pain-specific processing measured using a previously validated neural marker for evoked pain [146]; (ii) modulating affective/cognitive-evaluative systems traditionally mediating stress and primary defensive behavior in mammals [6,59,66,106,130,133,158,159] (in line with previous social touch effects [24,27,40,162]); and (iii) engaging somatosensory regions of

the held hand (see [55]), which may interfere with central nociceptive-specific processes [67] measured using time-series functional connectivity.

MATERIALS AND METHODS

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 [91,93]). All participants and their male partners gave 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 timeframe of data collection for this study was October 2012 to June 2013.

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 analog scales (VAS) to be used during the scanner session [122]. 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 [91]). 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 (e.g., [69,70,91,93]) and it is considered normative [122]. It is not advised to use scales that mix non-painful and painful sensations. Following Price and others [30,63,69,70,119–123], 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” (e.g., 3rd degree burns over the whole body). As in previous studies [69,70,91,93], 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 [63,85]. 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 [69,157] 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 [84] and that human pain perception thresholds are in the range of 45-46°C [123].

During the main fMRI session, we assessed brain and behavioral responses during two experimental conditions of interest (“baseline” condition (a) and “handholding” condition (b)), following an a-b-b-a run experimental design (Figure 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 (see Figure 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. Additionally, 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 two runs per condition (4 trials per run); therefore, the number of painful stimulations and the temperature was 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 [82,87,91,93–97,126,147,157,167]. Heat painful stimulations were administered to the volar surface of the participants' left forearm using an MRI-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 (pre-marked) 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?", i.e., 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.

Further, 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 papers on separate experimental tasks of this study (c.f., [91,93]).

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 two runs per condition (4 trials each) (Figure 1). During condition "a" the participant received pain without handholding support (holding an inert rubber device); during condition "b" the participant was holding their partners' hand (left hand of participant holding left hand of partner). We used average measures of pain intensity and

unpleasantness for all trials per condition (i.e., 8 trials for handholding and 8 trials for baseline). Paired-samples t-test were computed in MATLAB 2016 to assess within-group effects of handholding on pain intensity and unpleasantness. We computed an average measure of emotional comfort for the baseline and handholding condition (2 measures, one after each run, per condition), respectively, and then computed paired-samples t-test on them. Correlation analyses were computed using Pearson's r (MATLAB 2016).

Analyses of fMRI data

MRI acquisition and preprocessing. Functional brain activity was measured using a Siemens TrioTim 3T scanner, covering the brain in 26 interleaved transversal slices (3.4mm isomorphic voxels), with a T2* weighted EPI GRAPPA sequence (TR = 1.3s, TE = 25ms, flip angle = 50°, FOV = 220mm). SPM8 was used for preprocessing for functional images, using a standard pipeline for motion correction, slice-time correction, spatial normalization to MNI space, and spatial smoothing of images using an 8mm FWHM Gaussian kernel. For spatial normalization, T1 structural MPRAGE images (1mm isomorphic voxels) were first coregistered 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 2x2x2mm. Regarding motion correction, translation and rotation estimates (x , y , z) were less than 2 mm or 2°, respectively, for all the participants.

First level single-subject fMRI analyses. We used a GLM analysis approach as implemented in SPM8 software to estimate, for each subject, brain responses to pain during (a) single trials for the baseline and handholding conditions to be used in the whole-brain multilevel mediation model and (b) 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 responses (NPS [146]) for each subject and condition. Modeling the data considering the two halves of painful stimulation separately provides greater temporal resolution by allowing effects to be examined early and late in the stimulus epoch (please see [39,147]). We chose our approach because: (1) we were interested in studying NPS effects on both phases of the pain experience for two reasons: (a.) we had repeatedly observed that placebo analgesia exerted stronger effects in later (as opposed to earlier) phases of the pain trial [39,147] and also (b.) to ensure that all events (i.e., 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 [39,95,124,147]), 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.

For both baseline and handholding conditions, either single-trial pain regressors or a regressor modeling all pain trials for each condition were 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. Lastly, 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/canlab/MediationToolbox>).

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 detailed in previous articles, e.g., [93,97], 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 [146] 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, i.e., first half pain, second half pain, anticipation and pain ratings), we computed the cross product of the vectorized activation contrast image (β_{map}) with the NPS pattern of voxel weights ($NPS-\omega_{\text{map}}$), i.e., $\beta_{\text{map}}^T NPS-\omega_{\text{map}}$, yielding a continuous scalar value for each person and condition (baseline and handholding).

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 [79,93]. We then tested relationships between Condition (Handholding vs. Baseline), single-trial pain-evoked brain activation, and pain intensity and unpleasantness ratings across individual trials using multilevel mediation analysis [8]. Multilevel mediation analysis identifies three steps in a potential mechanistic pathway underlying handholding effects: (1) brain regions that show activity increases or decreases during handholding (Path *a*), (2) brain regions that predict changes in pain intensity/unpleasantness (Path *b*), when controlled for Path *a*, and (3) brain regions that formally mediate the relationship between condition (handholding vs. baseline) and reductions in pain intensity/unpleasantness (Path *a*b*), thus significantly reducing the strength of the direct Path *c*. We were specifically interested in Path *a*, showing activation reductions during handholding (vs. baseline), and path *a*b* of significant brain mediators of the effect of handholding on reducing pain unpleasantness. Resulting activation maps were thresholded at $q < 0.05$ FDR-corrected within an extensive whole-brain gray-matter mask including 352,328 voxels (corresponding to a voxel threshold of $p = .001$) and across mediation paths [8,79,93]. To facilitate interpretation of the functional maps, adjacent voxels were displayed at thresholds of $p = .005$ and $p = .01$ uncorrected.

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 to 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 ($a*b$ for intensity and unpleasantness), we calculated the similarity with each of the 7 major cortical networks in Yeo and colleagues [161]. We used a Dice coefficient [37] metric normalized across networks to reflect the percentage of significant voxels in each map (FDR $q < .05$) that fell within each network. We compared this with two meta-analyses of working memory, a widely studied cognitively demanding task that has shown some of the strongest 'distraction' effects on pain [16,17]. 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.

NPS-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 analysis [113] but is focused on changes related to sustained affective state across the entire run, and uses the NPS response (moment-by-moment, i.e., NPS response TR-by-TR time series regressor) as a "pattern of interest" rather than a single region (e.g., [7]). We used a GLM 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 brain [146]). Results were corrected for multiple comparisons $q < 0.05$ FDR within a whole-brain mask excluding NPS voxels.

RESULTS

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]) (Figure 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 [142], $r = 0.44$, $p = 0.016$ [N=30]) (Figure 1) and a trend (significant one-tailed) toward higher perceived closeness with the romantic partner (the Inclusion of Other into the Self, IOS [5], $r = 0.345$, $p = 0.085$ [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".

Handholding effects on acute brain responses to pain

Handholding reduces Neurologic Pain Signature (NPS) responses during pain. We divided the painful period into early and late phases (5.5 sec each) in order to study handholding effects on both phases. Previous work on placebo effects has shown stronger placebo effects later rather than earlier in the trial [39,147]. 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 of 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 Figure 1 for a more extensive visualization of heat-evoked brain responses in this task). 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 NPS 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: $t = -0.86$, $p = 0.40$) (Figure 2). These findings support the sensitivity and specificity of the NPS for pain, in line with more extensive validations published previously (e.g., [167]; for review, see [80,155]).

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*: $t = 2.04$, $d = 0.37$, $p = 0.05$). NPS 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 [167], cognitive reappraisal [156], reward [11], knowledge about drug-delivery context [146,167], or perceived control [14]. 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 [167].

Handholding increases time series connectivity between NPS, primary somatosensory (SI) and default mode network (DMN) 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 [113] 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 (e.g., [7]). We restricted our analysis to brain voxels outside the NPS (the NPS covers approximately 12% of the brain [146]).

Handholding significantly increased time-series correlations (across the entire run) between NPS responses and “default mode” network regions including medial prefrontal cortex, posterior cingulate cortex (PCC) and precuneus, temporo-parietal junction (TPJ), as well as the ventral striatum (accumbens) and middle temporal gyrus (Supplementary Table 1 and Figure 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, Figure 3). Increases in connectivity between NPS and SI during handholding were significantly associated with greater pain unpleasantness relief across individuals ($r = .382$, $p = .037$); the same trend was observed for pain intensity ($r = .312$, $p = .094$). 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 re-evaluating 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 are 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.

Pain-evoked brain activation reductions mediating reductions in pain intensity and unpleasantness during handholding. Though 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 [10,62,83,88,89,93,95,97,125,126,156,157]. To identify the brain systems that most strongly mediate handholding effects on pain reduction, we ran whole-brain multi-level mediation analyses across trial-by-trial estimates of brain and behavioral responses during pain [8,145,149]. 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; [8,9]). 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 [8,9,75,145,149].

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 ACC, dorsal and ventral lateral prefrontal cortex, thalamus, dorsal caudate, periaqueductal grey matter (PAG), amygdala, 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 (OFC, DMPFC, superior temporal gyrus, and temporal pole) ($q < 0.05$ FDR corrected, gray matter mask) (Supplementary Table 2, Figure 4; Supplementary Figure 2).

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, i.e., the dorsal/rostral ACC, anterior insula, right DLPFC/VLPFC (ventrolateral prefrontal cortex), 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, Figure 4; Supplementary Figure 2).

Significant mediators of pain unpleasantness (Path $a*b$, unpleasantness model) partially overlapped with mediators of pain intensity, and included rostral/dorsal ACC/SMA regions, subgenual ACC, DLPFC, VLPFC and VMPFC, OFC, ventral anterior insula, and middle temporal gyrus (Supplementary Table 4, Figure 4; Supplementary Figure 2). 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 (Figure 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 touch [55] and in cortico-cortical inhibition of pain by touch [67]; (5) finally, regions significantly involved in pain and affect regulation (i.e., DLPFC, VLPFC, rostral ACC [18,153,154], affective value and meaning (VMPFC and adjacent OFC [128,129,164,165]), and a specific circuit traditionally associated with stress and defensive behaviors (including VMPFC, subgenual ACC, PAG and AMG, reviewed in [130]), underpinned touched-related analgesia.

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 Default Mode (DMN) or Limbic network. There was also overlap with the Fronto-parietal network (FPN, ~30%) and Ventral Attention network (vAttn, ~10%). These are shown in the polar plots in Supplementary Figure 3, and values are in Supplementary Table 5. We compared this with two meta-analyses of working memory, a widely studied cognitively demanding task that has shown some of the strongest 'distraction' effects on pain [16,17]. For both [148,160] 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 FPN (~30-50%) and dorsal attention network (DAN, ~25-35%), with some overlap with vAttn (~10%) (Supplementary Figure 3 and Supplementary Table 5). 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 Figure 3). The handholding maps were similar with one another ($r = 0.71-0.96$), and the two working memory maps were similar ($r = 0.94$), but the handholding and working memory maps shared little overlap ($r = 0.22$ to 0.44).

DISCUSSION

This study is the first to show: (i) social touch effects on brain responses to pain (as opposed to pain anticipation [25,27]; (ii) social touch effects on a validated measure that tracks pain specifically (NPS, [146]) and not other affective events; (iii) potential mechanisms of how social touch reduces pain intensity and unpleasantness via 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. Many interventions have been studied behaviorally including pharmacological, social, and placebo interventions, and many have significant effects in reducing pain. However, the brain mechanisms via 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, since handholding involved reductions in NPS pain-specific (nociceptive) processing, whereas placebo analgesia has been systematically observed to not cause NPS reductions [167]. 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 (e.g., [20,27,48,53]) as it is a common natural form of expressing support and affection in times of struggle, pain and suffering ([56,57,135,137,140,150]) and has been associated with reconciliation and soothing behaviors [144]. Furthermore, handholding reduces autonomic arousal and reports of anxiety [27]. 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 prefrontal cortex/subgenual cingulate, hypothalamus, amygdala/hippocampus, and periaqueductal gray matter [6,59,66,106,130,133,158,159]. 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 [93], 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 [86]. 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 [44,55,104]. Also, although our study shows some parallelisms with studies investigating the effects of observing pictures of the romantic partner while receiving pain [101,162], we do not know to which degree these interventions involve very similar mechanisms or have the same impact on pain processing, as they have never been directly compared.

Handholding reduces nociceptive-specific (NPS) brain responses during pain

The NPS [146] 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 [14,81,92,93,103,146] 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 [21,81,92,103,146]. 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 [22,26,27,72,100]. Importantly, other pain regulation strategies such as placebo and cognitive self-regulation fail to downregulate this nociceptive-specific marker [156,167] indicating that handholding vs. other more purely cognitive strategies may at least partially differ in their mechanism of action.

Handholding increases NPS-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 [33,67,125]. Our findings propose a role for SI in cortico-cortical 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 [105]. Social and affective context can strongly influence touch pleasantness [43,44,104,143] and brain

processing of touch at sensory integration levels (e.g., [42,44,76,108]), particularly in SI [55]. Gazzola and colleagues [55] 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.

Further, handholding increases functional connectivity between the nociceptive process captured by the NPS marker and the DMN, particularly the PCC/precuneus region and medial prefrontal cortex. 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 [3,4,36,60,61,136,138,166]. In our study, regions directly involved in social cognition such as the temporal cortex and TPJ [1,2,54,131,132,163,166] 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 two partners in this handholding-pain context [57].

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 [29,92–95,97,116,124,146], 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. Besides this circuit, 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 [6,59,66,106,130,133,158,159]; 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 [115,147] and cognitive reappraisal of negative emotions [15,38,110–112]. Also, most of these prefrontal and OFC regions mediating reductions in pain intensity and unpleasantness are not usually activated by nociceptive stimulation [68,116]; these regions have been involved in attention control and

orientation, maintenance of relevant representations of stimuli, social/affective meaning, value and reward properties associated to stimuli and situations [12,32,34,35,52,73,117,118,129]. These regions, and not the NPS marker, directly mediate reductions of reported pain during handholding, suggesting that changes in cognitive/affective regulation circuits is critical for reductions of reported pain in this context, in line with previous studies [26,27,56,57].

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 [40]), did not evoke significant attenuation of pain [27,56]. And although early studies suggested stranger handholding mildly attenuated responses to threat of shock [24,27], a recent replication involving a large representative sample revealed little or no stranger effect [25]. This may suggest that the degree of closeness between the two 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 [56–58]. 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 to 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. Last, our findings are not necessarily generalizable to men. Nevertheless, a recent study suggests that sex is not a relevant moderator of handholding effects [25]. We focused on women as a first step because they are at greater risk of clinical, postoperative and procedural pain [51] and have shown stronger brain, psychological and physiological responses to negative affective stimuli [141,152].

In conclusion, handholding elicits analgesia via 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.

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The authors declare no conflict of interests.

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FIGURES

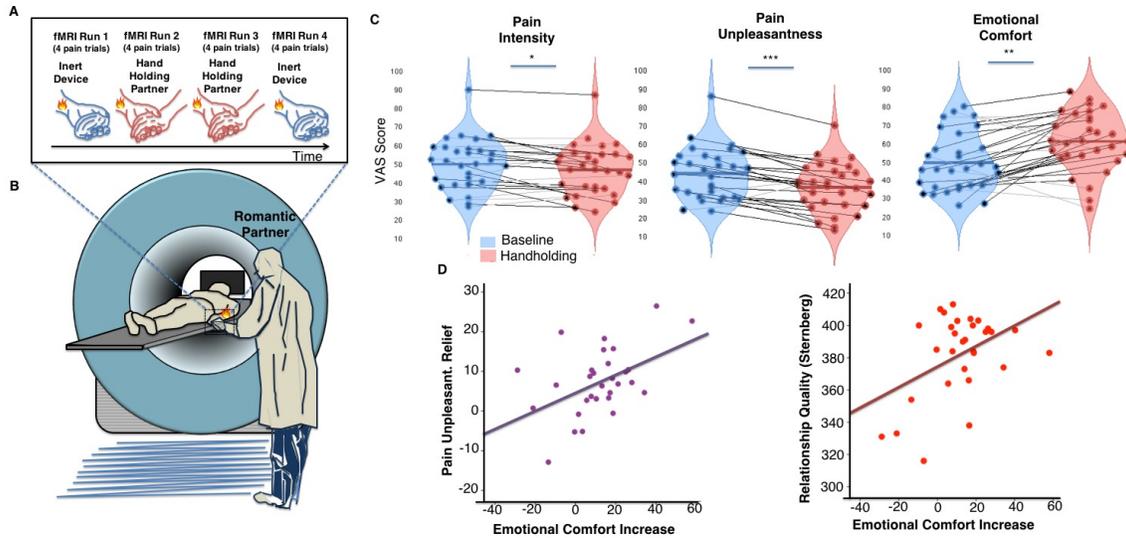


Figure 1. Experimental design: graphic representation of run/trial structure, experimental setting and behavioral results. **A.** Figure 1A represents the run/trial structure. **B.** Figure 1B represents the experimental setting. The female partner receives painful heat stimulation while being scanned; the male partner is providing support by holding her hand in runs 2 and 3. **C.** Figure 1C shows reductions in pain intensity and pain unpleasantness and increases in emotional comfort during handholding (blue: baseline condition, red: handholding condition -see main text results for summary statistics). **D.** Figure 1D illustrates significant positive correlations between (i) greater emotional comfort and greater pain unpleasantness relief during handholding (vs. baseline); and between (ii) greater emotional comfort increases during 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.

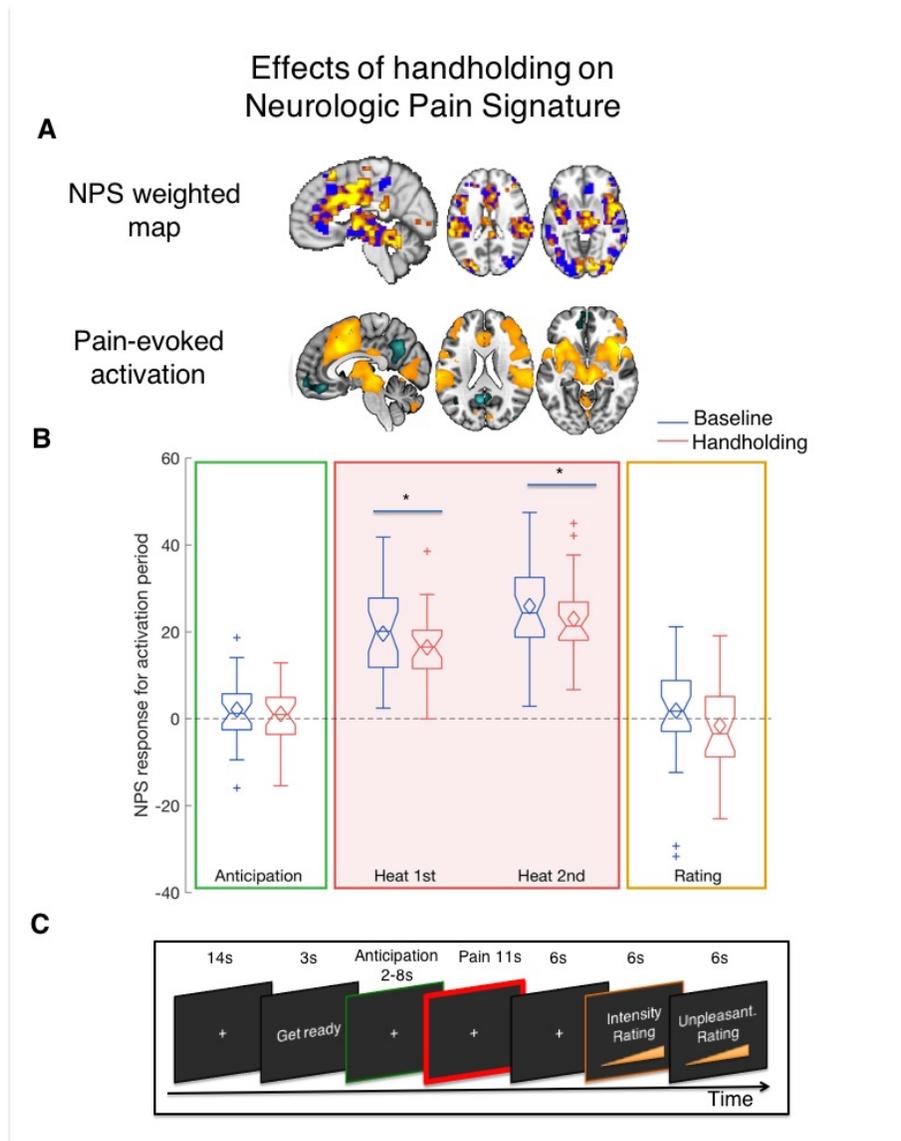


Figure 2. Neurologic pain signature (NPS) responses during baseline (blue) and handholding (red) conditions. A. Illustration of the NPS brain map of voxel weights and pain-evoked brain activation and deactivation responses during this task. **B.** Box plots represent NPS responses during anticipation, early pain (first half of heat period), late pain (second half of heat period), and pain ratings. Significant NPS responses were circumscribed to early and late pain periods and were non-significant during anticipation and pain rating periods. Handholding significantly reduced NPS responses for early and late pain periods (see main text for summary statistics). **C.** Figure C illustrates the trial structure and durations for the periods presented above.

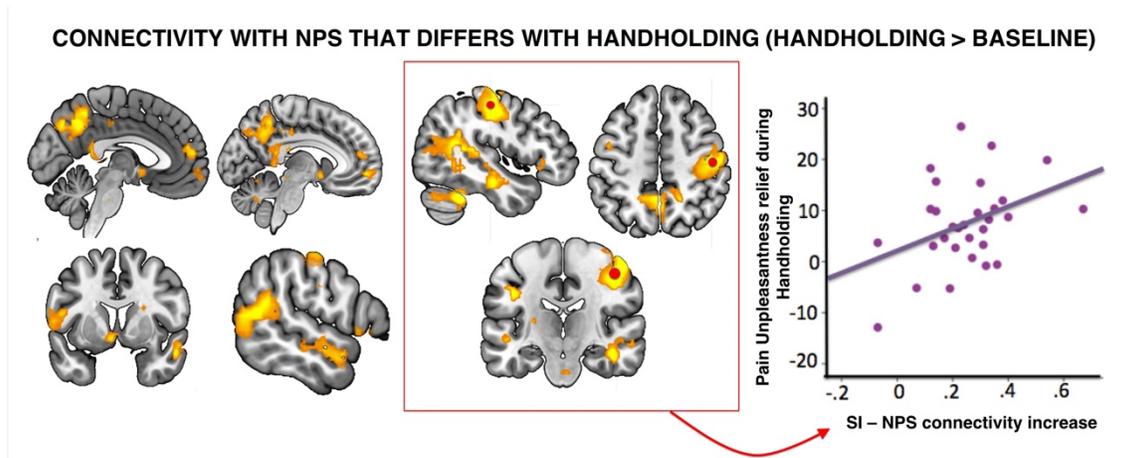


Figure 3. NPS connectivity during handholding (vs. baseline). Brain regions showing significantly greater time-series correlation with the NPS (Neurologic Pain Signature) during handholding (vs. baseline) runs. The red circle represents the location of a 6-mm diameter sphere that was placed in the peak 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).

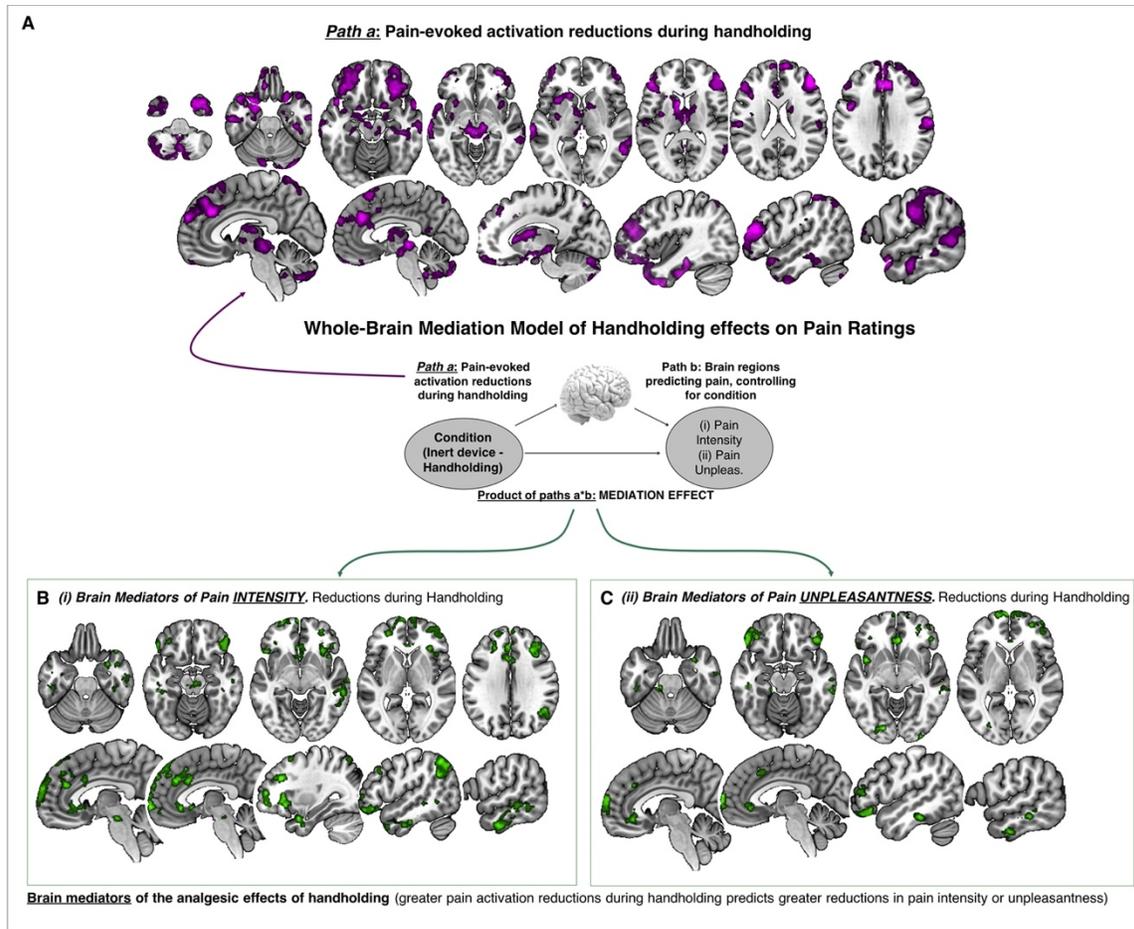


Figure 4. Whole-brain multilevel mediation results. A. Illustration of Path *a* effects, i.e., effects of condition (handholding vs. baseline) on brain responses to pain. Brain image maps display significant ($q < .05$ FDR corrected, gray matter mask) brain activation reductions in regions including DLPFC and VMPFC, ACC, medial prefrontal cortex, OFC, thalamus, secondary somatosensory cortex, amygdala, PAG, temporal cortices and cerebellum. **B.** Brain mediators of handholding effects on pain intensity, i.e., greater pain-evoked brain activation reductions in these regions predict greater pain intensity reductions during handholding (see also Supplementary Table 3). **C.** Brain mediators of handholding effects on pain unpleasantness, i.e., greater pain-evoked brain activation reductions in these regions predict greater pain unpleasantness reductions during handholding (see also Supplementary Table 4).

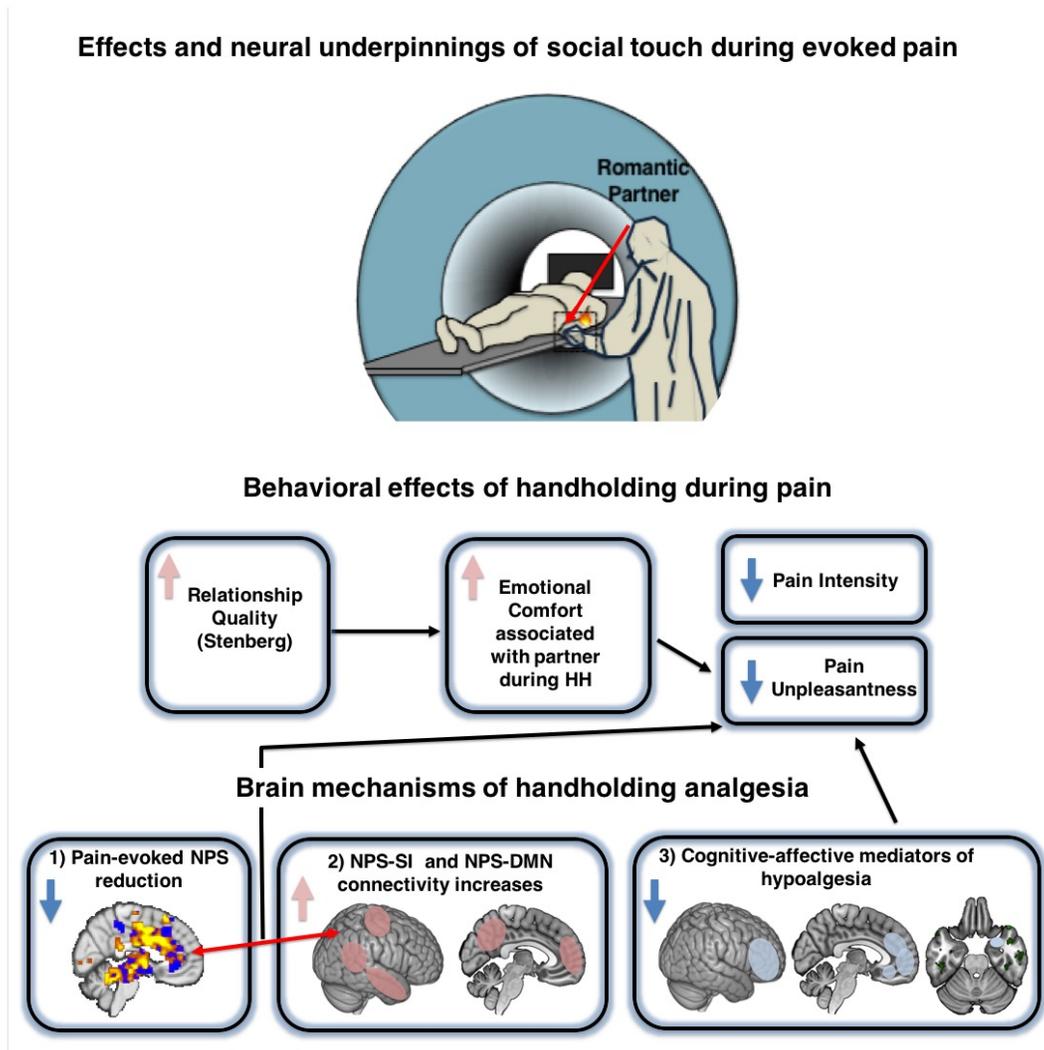


Figure 5. Effects and neural underpinnings of social touch by the romantic partner on evoked pain responses. The black arrows indicate significant positive relationships and the red arrow indicates a significant positive time series correlation between moment-by-moment NPS (neurologic pain signature) responses and regions in SI (primary somatosensory cortex of the held hand), TPJ (temporo-parietal junction) and other temporal regions and core regions of the default mode network (i.e., PCC and medial prefrontal cortex). Significant mediators of hypoalgesia during handholding include regions involved in stress/defensive behavior across mammals, and cognitive-affective modulators of affective stimuli including lateral and medial prefrontal cortex regions, subgenual/rostral ACC and amygdala.

SUPPLEMENTARY MATERIAL

Supplementary Tables

Supplementary Table 1. Regions showing significant differences in functional connectivity with the NPS process (across the run; handholding runs>baseline runs) ($q < .05$ FDR-corrected, gray matter mask)

Region/s	Peak coordinate	t-score	p-value
SI, R post-central gyrus	48, -20, 54	5.25	.00001
R PCC/precuneus	2, -57, 40	5.90	.000001
L PCC/precuneus	-7, -57, 38	4.14	.00036
L DMPFC	-5, 50, 16	3.90	.00070
R DMPFC	4, 57, 10	4.51	.00009
VMPFC	-7, 56, -4	4.24	.00020
R TPJ/ angular gyrus	49, -54, 16	4.37	.00051
L TPJ/supram./angular gyrus	-64, -49, 24	6.24	.0000008
Middle temporal gyrus	54, 4, -22	5.78	.000002
R Cerebellum	46, -47, -32	5.16	.000015
L Cerebellum	-38, -66, -38	4.24	.00020
L Ventral Striatum (Accumbens)	-7, 7, -8	4.18	.00024

SI, primary somatosensory cortex. R, right. L, left. PCC, posterior cingulate cortex. DMPFC, dorsomedial prefrontal cortex. VMPFC, ventromedial prefrontal cortex. TPJ, temporoparietal junction. Supram., supramarginal gyrus.

Supplementary Table 2. Path a, significant brain regions ($q < .05$ FDR-corrected, gray matter mask) showing pain-evoked activation reductions during handholding vs. baseline (positive values indicate pain activation reductions during handholding)

Region/s	Peak coordinate	z-stat (path a)	p-value
R DLPFC	46, 40, 20	4.55	.000005
L DLPFC	-48, 34, 16	5.01	.0000005
L precentral gyrus	-44, 2, 30	4.15	.00003
R OFC	34, 34, -16	4.05	.00005
L OFC	-32, 38, -20	3.94	.00007
OFC/gyrus rectus	-8, 36, -28	4.49	.000007
R MPFC	8, 44, 44	5.12	.0000003
L MPFC	-8, 40, 34	4.04	.00005
R ACC/paracingulate	2, 34, 30	4.85	.000001
L Insula	-34, 14, 4	4.05	.000049
SI/SII	62, -18, 32	4.39	.00001
PAG-brainstem	-6, -26, -6	4.44	.000008
L AMG-HFC	-24, -4, -24	4.11	.00004
Sup. Temporal gyrus/temporal pole	-48, 14, -20 28, 10, -28	4.82 4.13	.000001 .00005
Inferior Temporal gyrus	30, 10, -44	3.97	.00007
L Caudate/Thalamus	-10, 2, 14	4.30	.00001
	-8, 8, 12	5.74	.000000009
Cerebellum	-42, -74, -50	4.33	.00001

SI, primary somatosensory cortex. R, right. L, left. PCC, posterior cingulate cortex. DMPFC, dorsomedial prefrontal cortex. VMPFC, ventromedial prefrontal cortex. TPJ, temporoparietal junction. Supram., supramarginal gyrus.

Supplementary Table 3. Path ab, Intensity model. Significant brain regions ($q < .05$ FDR-corrected, gray-matter mask) mediating pain intensity reductions during handholding (for path a, positive values indicate activation reductions during handholding; for path b, positive numbers indicate brain activation reductions that correlate with pain intensity reductions during handholding vs. baseline).

Region/s	Peak coordinate	Path ab z-stat /p-value	Path a z-stat /p-value	Path b z-stat / p-value
R DLPFC	32, 32, 28	4.06/.00001	1.06/.290	.02/.970
R VLPFC	32, 54, 8	4.03/.00005	.487/.626	-1.03/.302
Insula R	34, 30, 8	3.94/.00007	2.12/.033	-.02/.979
R VMPFC/DMPFC	8, 68, 8	4.18/.00002	.31/.759	-.69/.485
L VMPFC	-3, 67, -5	4.17/.00003	.99/.318	.60/.545
ACC/sup. frontal gyrus	-4, 36, 30	4.03/.00005	4.16/.00003	1.10/.270
Subgenual ACC	0, 14, -4	3.93/.00008	-.48/.626	-.77/.430
L OFC	-36, 36, -12	3.94/.00008	2.11/.034	.09/.924
L middle/inf. frontal gyrus	-28, 48, 6	4.03/.00005	-.16/.866	.11/.916
Brainstem/midbrain	6, -22, -18	4.26/.00002	1.42/.155	.92/.360
Parietal/angular gyrus	50, -58, 48	4.06/.00005	2.29/.021	2.72/.006
R middle/inf. temporal gyrus	62, -12, -30	4.17/.00003	2.37/.017	1.22/.219
R middle temporal gyrus	62, -32, -8	4.00/.00006	1.53/.126	.30/.766

R, right; L, left; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; ACC, anterior cingulate cortex; sup., superior; OFC, orbitofrontal cortex; inf., inferior.

Supplementary Table 4. Path ab, Unpleasantness model. Significant brain regions ($q < .05$ FDR-corrected, gray-matter mask) mediating pain intensity reductions during handholding (for path a, positive values indicate activation reductions during handholding; for path b, positive numbers indicate brain activation reductions that correlate with pain intensity reductions during handholding vs. baseline).

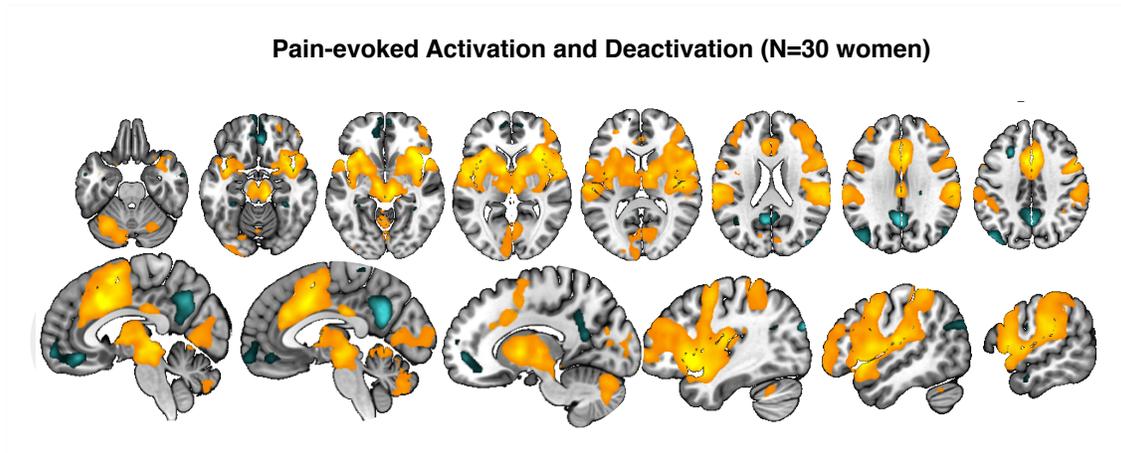
Region/s	Peak coordinate	Path ab z-stat /p-value	Path a z-stat /p-value	Path b z-stat /p-value
ACC/SMA	-8, 12, 50	3.95/.00007	.634/.520	.157/.874
L DLPFC	-44, 36, 18	3.98/.00006	2.61/.008	1.27/.200
L DLPFC	-38, 36, 38	4.02/.00005	1.68/.092	.53/.592
R MPFC	6, 64, 16	3.99/.00006	1.52/.127	.38/.698
L MPFC	-2, 70, 8	4.30/.00001	1.10/.268	.99/.318
L OFC	-36, 38, -16	4.03/.00005	3.06/.002	2.24/.024
L Insula	-42, 8, -8	4.24/.00002	.60/.544	1.48/.138
Subgenual ACC	2, 34, -8	4.29/.00001	.22/.819	-1.09/.274
R DLPFC/VLPFC	32, 54, 8	3.95/.00007	.51/.605	-.290/.771
R middle temporal gyrus	62, -30, -12	4.12/.00003	1.75/.080	1.04/.294
L AMG	-18, 4, -30	4.00/.00006	3.59/.0003	1.04/.293
L middle occipital gyrus	-20, -86, -6	3.96/.00007	.23/.817	-.33/.735
Cerebellum	-16, -32, -22	4.20/.00002	-.19/.84	1.88/.059

ACC, anterior cingulate cortex; SMA, supplementary motor area; DLPFC, dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; VLPFC, ventrolateral prefrontal cortex; AMG, amygdala.

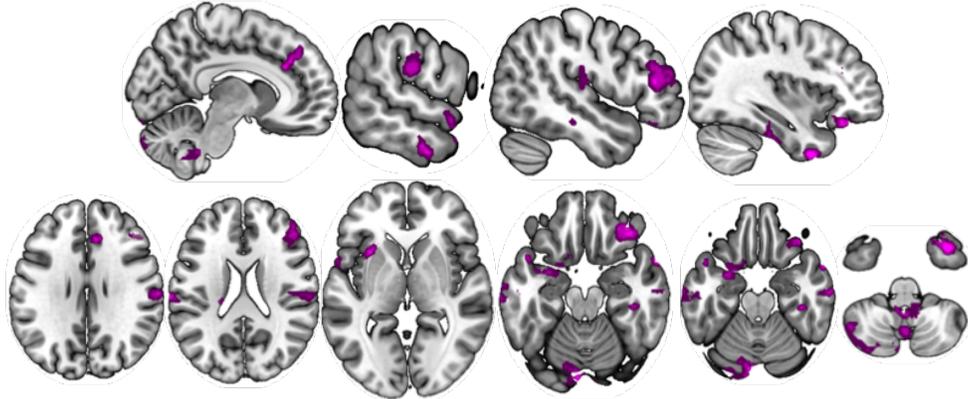
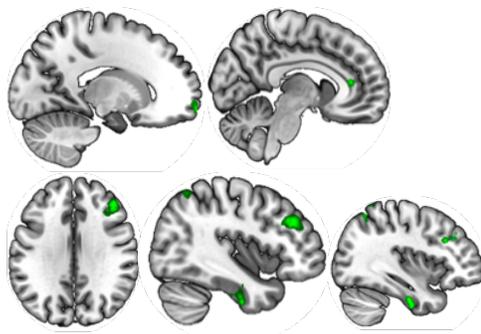
Supplementary Table 5. Normalized dice coefficient table identifying similarity between handholding effects and cognitive demand (i.e., distraction) as measured using previously published working memory meta-analyses

Network	Handholding effects on pain			Working memory	
	Intensity a*b	Handholding Path a	Unpleas. a*b	WM meta 2003	Neurosynth RI
Visual	1	1	3	6	0
Somatomotor	0	3	0	8	0
dAttention	4	7	1	25	36
vAttention	14	9	10	10	11
Limbic	15	32	17	7	0
Frontoparietal	29	28	36	29	52
Default	38	20	34	15	1

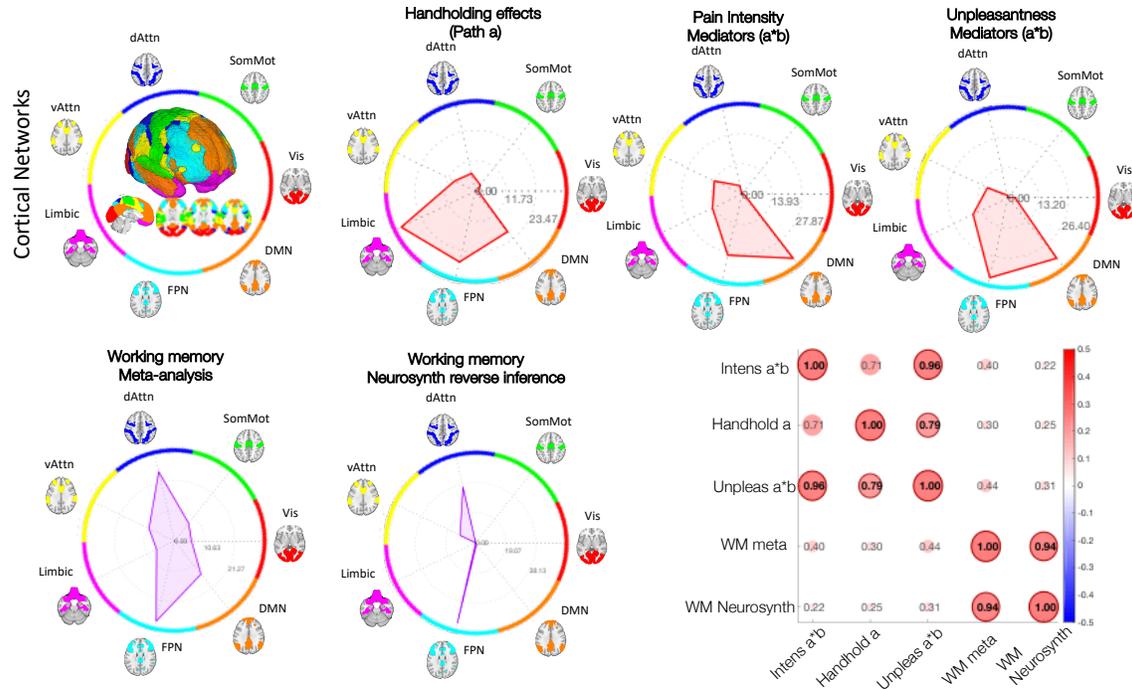
Measure of the similarity between handholding effects and other manipulations of cognitive demand and attentional diversion, i.e., 'distraction', as measured using working memory meta-analyses. For the handholding effects (Handholding path a, handholding vs. holding pneumatic device on brain activity during pain) and the mediation effect maps (a*b for intensity and unpleasantness), we calculated the similarity with each of the 7 major cortical networks in Yeo et al. 2011. We used a Dice coefficient metric, normalized across networks, to reflect the percentage of significant voxels in each map (FDR $q < .05$) that fell within each network. Path a: Normalized dice coefficients between significant brain regions ($q < .05$ FDR-corrected) in path a and each of the 7 networks in Yeo et al., 2011. Intensity a*b: Normalized dice coefficients between path a*b for the significant regions in the pain intensity model ($q < .05$ FDR-corrected) and each of the 7 networks in Yeo et al., 2011. Unpleasantness a*b: Normalized dice coefficients between path a*b for the significant regions in the pain unpleasantness model ($q < .05$ FDR-corrected) and each of the 7 networks in Yeo et al., 2011. WM meta 2003: Normalized dice coefficients between significant regions in the WM (working memory) meta-analysis (Wager and Smith, 2003) and each of the 7 networks in Yeo et al., 2011. Neurosynth RI: Normalized dice coefficients between Neurosynth RI ('reverse inference') map for the term working memory (Yarkoni et al. 2011) and each of the 7 networks in Yeo et al., 2011.

Supplementary Figures

Supplementary Figure 1. Pain-evoked activation (warm colors) and deactivation (cold colors) during heat pain trials.

Path a: Pain-evoked activation reductions during handholding (entire pain period)**Path a*b: Pain-evoked activation reductions during handholding (entire pain period)****Brain mediators of handholding on
pain INTENSITY reductions****Brain mediators of handholding on pain
UNPLEASANTNESS reductions**

Supplementary Figure 2. Whole-brain multilevel mediation results (entire pain period). Upper panel. Illustration of Path *a* effects, i.e., effects of condition (handholding vs. baseline) on brain responses to pain (entire pain period). Brain image maps display brain activation reductions ($p < 0.001$ uncorrected) in regions including DLPFC and ACC, medial prefrontal cortex, OFC, secondary somatosensory cortex, amygdala, temporal cortices and cerebellum. Lower panels. Brain mediators of handholding effects on pain intensity, i.e., greater pain-evoked brain activation reductions in these regions predict greater pain intensity reductions during handholding ($p < 0.001$ uncorrected). C. Brain mediators of handholding effects on pain unpleasantness, i.e., greater pain-evoked brain activation reductions in these regions predict greater pain unpleasantness reductions during handholding ($p < 0.001$ uncorrected).



Supplementary Figure 3. Normalized dice coefficient representation using polar plots and a correlation matrix identifying similarity between handholding effects and cognitive demand (i.e., distraction) as measured using previously published working memory meta-analyses (Wager and Smith, 2003; Yarkoni et al., 2011). This study did not compare handholding to other strategies, but it is possible to compare the maps we identified of handholding effects on brain responses to pain 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. holding pneumatic device on brain activity during pain) and the mediation effect maps (a*b for intensity and unpleasantness), we calculated the similarity with each of the 7 major cortical networks in Yeo et al. 2011. We used a Dice coefficient metric, normalized across networks to reflect the percentage of significant voxels in each map (FDR $q < .05$) that fell within each network. These results are shown in the polar plots. We compared this with two meta-analyses of working memory (Wager and Smith, 2003 and Yarkoni et al., 2011), a widely studied cognitively demanding task that has shown some of the strongest ‘distraction’ effects on pain (Buhle and Wager, 2011; Sprenger and Buchel, 2015). Furthermore, to estimate the overall similarity between hand-holding and working memory across cortical networks, we calculated the correlation matrix across normalized Dice coefficients for all images reported in the correlation matrix.