Social rejection shares somatosensory representations with physical pain

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How similar are the experiences of social rejection and physical pain? Extant research suggests that a network of brain regions that support the affective but not the sensory components of physical pain underlie both experiences. Here we demonstrate that when rejection is powerfully elicited—by having people who recently experienced an unwanted break-up view a photograph of their ex-partner as they think about being rejected—areas that support the sensory components of physical pain (secondary somatosensory cortex; dorsal posterior insula) become active. We demonstrate the overlap between social rejection and physical pain in these areas by comparing both conditions in the same individuals using functional MRI. We further demonstrate the specificity of the secondary somatosensory cortex and dorsal posterior insula activity to physical pain by comparing activated locations in our study with a database of over 500 published studies. Activation in these regions was highly diagnostic of physical pain, with positive predictive values up to 88%. These results give new meaning to the idea that rejection "hurts." They demonstrate that rejection and physical pain are similar not only in that they are both distressing—they share a common somatosensory representation as well.

emotion | social pain | affective neuroscience | neuroimaging | psychological distress

Consider two scenarios. In the first, you spill a hot cup of coffee on your forearm and experience intense pain. In the second, you look at pictures of your former romantic partner, a person with whom you recently experienced an unwanted break-up; as you view each photo you feel rejected and experience another kind of "pain." On the surface, these two events seem quite distinct. Whereas the former involves a noxious bodily stimulus, the latter involves the termination of a social relationship. However, cultures around the world use the same language—words like "hurt" and "pain"—to describe both experiences (1), raising the question: How similar are social rejection and physical pain?

Several recent studies have attempted to address this issue by examining the neural overlap between physical pain and social rejection. The consensus that has emerged is that a network of brain regions that support the aversive quality of physical pain (the "affective" component), principally the dorsal anterior cingulate (dACC) and anterior insula (AI), also underlie the feeling of social rejection. In contrast, the brain regions that support the somatic representation of physical pain, and are most closely aligned with the "sensory-discriminative" component—including the operculo-insular region [i.e., secondary somatosensory cortex (S2) and dorsal posterior insula (dpINS)]—are not activated by social rejection and do not factor into current theorizing about the neural overlap between social rejection and physical pain (1, 2).

At first glance, these findings seem intuitive. Both social rejection and physical pain are distressing, and both the dACC and AI respond broadly to stimuli that elicit negative affect (3). However, being rejected, however distressing, seems different from physical pain; it does not result from the presence of a noxious bodily stimulus. Thus, failure to observe activations in brain regions that support the somatic representation of physical pain in response to rejection is not surprising.

As plausible as this rationale is, here we suggest an alternative: that the neural overlap between social rejection and physical pain is more extensive than current findings suggest. Specifically, we propose that experiences of social rejection, when elicited powerfully enough, recruit brain regions involved in both the affective and sensory components of physical pain.

This prediction is motivated by research indicating that the brain regions that support the sensory components of physical pain are more likely to become active in response to intensely painful stimuli (4–6, cf 7). This finding is noteworthy because extant fMRI research has induced feelings of rejection that may not be particularly intense. (One exception is ref. 8, which we mention in the *Discussion*.) For example, such studies have excluded participants from a computerized ball-tossing game called "Cyberball" (e.g., refs. 9–11), exposed them to rejection-themed paintings (12), or provided them with anonymous feedback that a stranger does not like them (13). Although these manipulations elicit distress, few would attribute to them the same level of intensity as the pain surrounding an unwanted romantic relationship breakup (14–16). Thus, it is possible that social rejection activates brain regions specific for somatic processes, but only when the stimulus is sufficiently intense (i.e., a rejection stimulus rated as intense as a physically painful stimulus on a comparable scale).

We tested this hypothesis by recruiting 40 individuals who felt intensely rejected as a result of recently experiencing an unwanted romantic relationship break-up (see *Methods*). Participants performed two counterbalanced tasks during functional MRI (fMRI) scanning: a Social Rejection task and a Physical Pain task (for design, see Fig. 1). Briefly, the Social Rejection task compared Ex-partner trials, in which participants viewed a headshot of their former partner and thought about their specific rejection experience, and Friend trials, in which participants viewed a headshot of a friend who was the same sex as their ex-partner and thought about a recent positive experience they shared with that person. The Physical Pain task also consisted of two types of trials: Hot trials, in which participants experienced noxious thermal stimulation on their left forearm, and Warm trials, in which participants experienced non-noxious thermal stimulation in the same area. Participants rated how they felt after each task trial using a five-point scale, with lower numbers reflecting more distress.

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Fig. 1. Time course of Social Rejection and Physical Pain trials. The Social Rejection and Physical Pain tasks each consisted of two consecutively administered runs of eight trials (i.e., 16 total trials). The order of the two tasks was counterbalanced across participants. (*A*) Each Social Rejection trial lasted 45 s and began with a 7-s fixation cross. Subsequently, participants saw a headshot photograph of their ex-partner or a close friend for 15 s. A cue-phrase beneath each photo directed participants to think about how they felt during their break-up experience with their ex-partner or a specific positive experience with their friend. Subsequently, participants rated how they felt using a five-point scale (1 = very bad; 5 = very good). To reduce carryover effects between trials, participants then performed an 18-s visuospatial control task in which they saw an arrow pointing left or right and were asked to indicate which direction the arrow was pointing. Ex-partner vs. Friend trials were randomly presented with the constraint that no trial repeated consecutively more than twice. (*B*) The structure of Physical Pain trials was identical to Social Rejection trials with the following exceptions. During the 15-s thermal stimulation period, participants viewed a fixation cross and focused on the sensations they experienced as a hot (painful) or warm (nonpainful) stimulus was applied (1.5-s temperature ramp up/down, 12 s at peak temperature) to their left volar forearm (for details, see *Methods*). They then rated the pain they experienced using a five-point scale (1 = very painful; 5 = not painful).

Results

Self-Report Distress. As expected, participants reported experiencing greater distress on Ex-partner trials (M = 1.72, SD = 0.36) than Friend trials [M = 4.23, SD = 0.41; $t(39) = -26.05$, $P < 0.001$]; and Hot trials (M = 1.88, SD = 0.57) than Warm trials [M = 4.46, SD = 0.52; $t(39) = -19.45$, $P < 0.001$]. Importantly, the increases in distress participants experienced on Ex-partner vs. Friend trials (M = −2.50, SD = 0.61) and on Hot vs. Warm trials (M = −2.59, SD = 0.84) were equivalent [$t(39) = -0.56$, ns], suggesting that the two tasks were matched in their subjective intensity (see Fig. 1 for a description of scale anchors).

Neural Overlap Between Social Rejection and Physical Pain. The study's main hypotheses concerned whether fMRI activity related to social rejection and physical pain would activate common regions within networks linked to the sensory and affective components of physical pain. We examined this issue by performing a conjunction analysis on the activation associated with social rejection (Ex-partner > Friend) and physical pain (Hot > Warm). Although our hypotheses were anatomically motivated, we set a statistical threshold that controls for the family-wise error rate (FWER) based on a cluster extent at $P < 0.05$ corrected across the whole brain ($P < 0.001$; 11 voxel extent threshold). This whole-brain analysis indicated that both types of experiences led to overlapping increases in activity in affective pain regions found in previous studies, including the dACC and AI. Critically, we also found overlapping increases in thalamus and right parietal opercular/insular cortex (i.e., S2), contralateral to the site of thermal stimulation (Fig. 2*A* and Table 1; see Tables S1 and S2 for the individual contrast results). A series of follow-up regression analyses that controlled for task order and several theoretically relevant variables [e.g., sex, rejection sensitivity (17), self-esteem (18), and the length of participants relationships with their former romantic partner and friend] did not substantively alter these findings.

Region of Interest Analyses. To further test our hypothesis, we ran a priori region of interest (ROI) analyses in pain-processing network regions defined by an independent localizer for physical pain. To identify regions that encode the intensity of physical pain, we contrasted Hot > Warm thermal stimulation of the left arm in a separate group of individuals ($n = 75$) drawn from three separate thermal pain studies (see *Methods*). This localizer identified a network of common physical pain regions, including

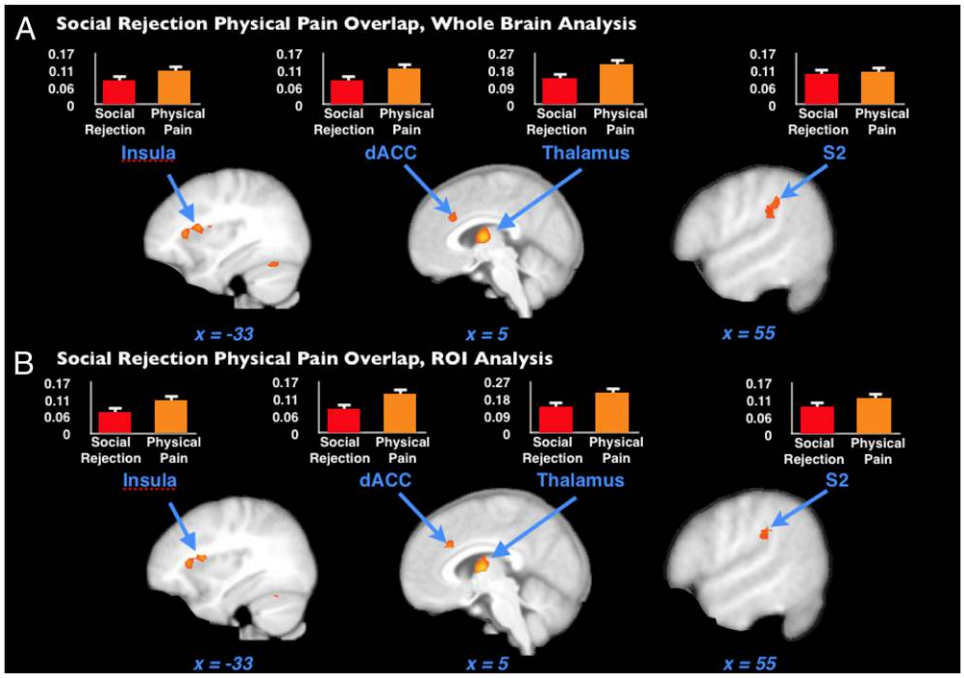

Fig. 2. Neural overlap between social rejection and physical pain. (*A*) A whole-brain conjunction analysis revealed that regions typically involved in both the affective [AI (−30, 11, 14); dACC (9, 26, 24)] and sensory [thalamus (6, −4, 7); S2 (62, −28, 36)] components of physical pain were also involved in response to social rejection (Ex-partner > Friend) and physical pain (Hot > Warm). (*B*) An ROI analysis performed on physical pain regions revealed overlap between social rejection and physical pain in regions similar to those identified by the whole-brain analysis [AI (−33, 11, 14); dACC (6, 26, 24); thalamus (6, −4, 7); S2 (59, −26, 24)]. Bar graphs demonstrate the β-values for social rejection (Ex-partner > Friend) and physical pain (Hot > Warm) extracted from each cluster. Error bars represent one SE. None of the β-values associated with social rejection differed significantly from the β-values associated with physical pain (all two-tailed paired sample t statistics < 1.75, all P values > 0.09).

the operculo-insular region, thalamus, dACC, and AI. Fig. 2*B* shows the conjunction of areas activated in the independent localizer and the physical pain and social rejection contrasts. The results again show that each of the pain intensity-encoding regions was activated in response to social rejection ($P < 0.05$ FWER-corrected) (Table 2).

Prior research has identified two regions in the operculo-insular region that are specifically involved in pain-related somatosensory processing: OP1, the most caudal area of the parietal operculum, and dpINS (19–23). To identify whether social rejection and physical pain coactivated these areas, we performed a priori ROI analyses on these regions (see *Methods* for details regarding ROI definition). As Fig. 3 illustrates, the overlap between social rejection and physical pain fell within both of these regions bilaterally ($P < 0.05$ FWER-corrected for each ROI) (see Fig. 3 *A* and *B* for statistics).

To rule out the possibility that the activations observed in these sensory pain ROIs were a result of testing participants on both the Physical Pain and Social Rejection tasks in a within-subjects design, we reran these ROI analyses on the subset of participants who engaged in the Social Rejection task before the Physical Pain task ($n = 19$). Consistent with our covariate analyses, which indicated that controlling for task order did not substantively alter the pattern of whole-brain results, these analyses revealed activity in both sensory pain ROIs (right OP1: 88 voxels; right dpINS: 54 voxels).*

Table 1. Activations associated with whole-brain conjunction analysis examining the overlap between social rejection (Ex-partner > Friend) and physical pain (Hot > Warm) at $P < 0.05$, FWER-corrected

Region of activation	Brodmann's area	*t*	Tal coordinates *x*	*y*	*z*	Voxels
Cluster 1		6.00	12	14	3	319
Anterior cingulate	32	4.37	9	26	24	33
Caudate		6.00	12	14	3	82
Caudate		4.86	−15	3	23	35
Caudate		4.05	12	−3	18	18
Caudate		3.91	15	20	14	10
Putamen		4.83	21	9	17	16
Thalamus		5.46	6	−4	7	124
Cluster 2		5.20	−21	−63	−14	170
Cerebellum		5.20	−21	−63	−14	164
Cerebellum		3.87	−9	−62	−6	6
Cluster 3		4.68	−30	11	14	105
Insula/claustrum		4.68	−30	11	14	53
Insula/claustrum		4.28	−30	3	12	11
Insula/inferior frontal gyrus	13	4.60	−36	23	8	32
Putamen		4.18	−18	2	9	9
Cluster 4	40	4.39	62	−28	36	74
Inferior parietal lobule	40	4.39	62	−28	36	64
Inferior parietal lobule	40	4.30	59	−29	24	10
Cluster 5	32	4.32	15	35	16	34
Anterior cingulate	32	4.32	15	35	16	29
Caudate		4.02	18	28	5	5
Cluster 6		3.95	−9	11	3	15
Caudate		3.95	−9	11	3	15
Cluster 7		3.75	9	−1	62	11
Superior frontal gyrus	6	3.75	9	−1	62	11

The coordinates listed next to each "cluster" represent the cluster's peak coordinate and are identical to the coordinates associated with the largest local maxima within each cluster. Local maxima associated with each cluster are indented and ordered alphabetically. The voxel count associated with each "cluster" represents the number of contiguous voxels observed in the entire region of activation; the voxel count associated with each local maxima represents the number of voxels attributed to each peak within the larger activation cluster.

Table 2. Activations associated with an ROI analysis examining the overlap between social rejection (Ex-partner > Friend) and physical pain (Hot > Warm) in pain-processing network regions defined by an independent localizer for physical pain at $P < 0.05$, FWER-corrected

Region of activation	Brodmann's area	*t*	Tal coordinates *x*	*y*	*z*	Voxels
Cluster 1		5.46	6	−4	7	124
Caudate		4.05	12	−3	18	13
Thalamus		5.46	6	−4	7	111
Cluster 2		5.20	−21	−63	−14	73
Cerebellum		5.20	−21	−63	−14	73
Cluster 3		4.60	−36	23	8	41
Inferior frontal gyrus	13	4.60	−36	23	8	33
Insula	13	4.53	−33	11	14	8
Cluster 4		4.31	6	26	24	16
Anterior cingulate	24	4.31	6	26	24	16
Cluster 5		4.15	59	−26	24	23
Inferior parietal lobule	40	4.15	59	−26	24	23
Cluster 6		3.72	36	28	5	6
Inferior frontal gyrus	45	3.72	36	28	5	6

The coordinates listed next to each "cluster" represent the cluster's peak coordinate and are identical to the coordinates associated with the largest local maxima within each cluster. Local maxima associated with each cluster are indented and ordered alphabetically. The voxel count associated with each "cluster" represents the number of contiguous voxels observed in the entire region of activation; the voxel count associated with each local maxima represents the number of voxels attributed to each peak within the larger activation cluster.

Pain-Specificity Analyses. To further test the specificity of these activations to pain-related somatic processing, we used a meta-analytic database of 524 studies to compare the frequency with which published studies of physical pain (24) led to activations within 10 mm of the peak coordinates in right and left OP1 and dpINS (see Fig. 3*C* for coordinates), in comparison with published studies on a range of tasks that do not involve physical pain or intense social rejection; the latter included studies of positive and negative emotion (25), cognitive-interference resolution (26), long-term memory encoding and retrieval (27), attention switching (28), and working-memory (29). Consistent with prior research, activations in OP1 [right hemisphere: $\chi^2(5) = 92.32$, $P < 0.001$; left hemisphere: $\chi^2(5) = 37.21$, $P < 0.005$] and dpINS [right hemisphere: $\chi^2(5) = 91.83$, $P < 0.001$; left hemisphere: $\chi^2(5) = 32.19$, $P < 0.01$] were selective for physical pain. As Fig. 3*C* illustrates, out of the 524 studies we examined, the positive predictive value for physical pain (i.e., the probability that a study involved physical pain given activation) was 0.88 in the right OP1, 0.74 in the left OP1, 0.87 in the right dpINS, and 0.75 in the left dpINS. In short, intense social rejection activated somatosensory regions that are strongly associated with physical pain, which are virtually never associated with emotion as typically studied.

*Although we did not observe bilateral activation in dpINS and OP1 in this subset of participants, we found no evidence of lateralization when we compared the β-values extracted from right and left OP1, and right and left dpINS (all, Fs < 0.318, ns). We suspect that failure to observe bilateral activations among this subset of participants in these ROIs may be an issue of power, as we observed bilateral activation in the full sample, which was double the size.

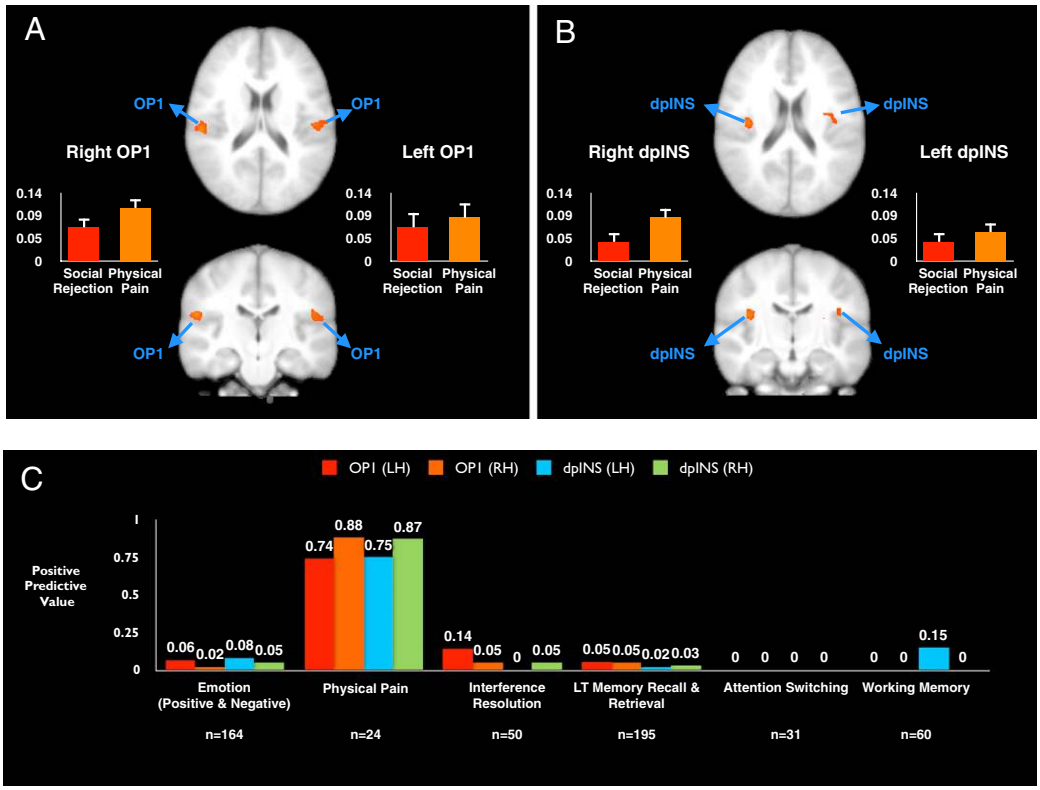

Fig. 3. Operculo-insular ROI analyses. The neural overlap between social rejection and physical pain in (*A*) OP1 [right hemisphere (RH): 46 voxels; $x = 56$, $y = -23$, $z = 21$, $t_{peak} = 3.52$; left hemisphere (LH): 43 voxels; $x = -48$, $y = -17$, $z = 21$, $t_{peak} = 2.97$) and (*B*) dpINS (RH: 24 voxels; $x = 39$, $y = -15$, $z = 18$, $t_{peak} = 2.85$; LH: 23 voxels; $x = -39$, $y = -9$, $z = 23$, $t_{peak} = 2.75$). Coordinates are in Talairach space. Bar graphs demonstrate the β-values for social rejection and physical pain in each ROI. Error bars represent one SE. We performed two separate repeated-measure ANOVAs using the β-values extracted from OP1 (Analysis #1) and dpINS (Analysis #2) ROIs. Each analysis included pain type (social vs. physical) and hemisphere (right vs. left) as within participant factors. These analyses revealed no significant main effects (OP1: all $F < 0.84$, all $P > 0.36$: dpINS: all $F < 2.64$, $P > 0.11$) or interactions (OP1: $F = 0.31$, $P = 0.58$: dpINS: $F = 2.25$, all $P > 0.14$). These findings indicate that it was not the case that one type of pain led to significantly greater activation compared with the other, or that the activations were lateralized to one side of the brain in these ROIs. (*C*) Bar graphs illustrating the results of a Bayesian analysis, which examined the specificity of the activation observed in OP1 (RH: $x = 56$, $y = -23$, $z = 21$; LH: $x = -48$, $y = -17$, $z = 21$) and dpINS (RH: $x = 39$, $y = -15$, $z = 18$; LH: $x = -39$, $y = -9$, $z = 23$) for physical pain. Bars represent the probability that a study activating a region within 10 mm of the peak coordinate in OP1 (red and orange bars) and dpINS (blue and green bars) belonged to that task category (i.e., the positive predictive value for each task type). Error bars represent one SE. "*n*" refers to the number of each type of study included in the meta-analysis.

Discussion

These results give new meaning to the idea that social rejection "hurts." Current theorizing suggests that the brain systems that underlie social rejection developed by coopting brain circuits that support the affective component of physical pain (1, 2, 9). The current findings substantively extend these views by demonstrating that social rejection and physical pain are similar not only in that they are both distressing, they share a common representation in somatosensory brain systems as well.

These findings offer new insight into how rejection experiences may lead to various physical pain disorders (e.g., somatoform disorders; fibromyalgia), highlighting the role that somatosensory processing may play in this process. They are also consistent with research on "embodiment," which suggests that somatosensory processing is integral to the experience of emotion (30–32), and the results of a recent study that observed activity in dpINS in response to a social rejection manipulation similar to the one used here (8). These results are also consistent with two recent studies indicating that biological vulnerabilities that predispose people to higher physical pain sensitivity are associated with activation in or around the somatosensory cortex in the Cyberball rejection task (33, 34), a task that has not previously revealed somatosensory activations (for review, see ref. 2). Still, it is unclear whether the activations observed in these prior studies were in pain-specific somatosensory areas.

The current results also have implications for basic research on emotion. Although the experience of social rejection is commonly accompanied by reports of various emotions (e.g., fear, sadness, anger, anxiety, and shame), it is generally assumed that these feelings cumulatively give rise to a unique experience of "social pain" (35–37). The results of the meta-analyses we performed in this study, which indicated that fMRI studies of specific emotions rarely activate OP1 and dpINS, are consistent with this view. Only 3 of 164 studies and 1 of 164 studies activated the left OP1 and right OP1, respectively, and only 3 of 164 studies activated each of the left and right dpINS; none of which are proportions significantly higher than expected by chance (cf, 25). Thus, the combined fMRI and meta-analysis results suggest that the distress elicited in response to intense social rejection may represent a distinct emotional experience that is uniquely associated with physical pain.

Our meta-analysis, which included multiple studies that contrasted high vs. low intensity nonphysical pain-related emotional stimuli, also demonstrates that it is not the case that any intense induction of emotion activates the S2/dpINS. This finding is consistent with research that has directly examined the relationship between (nonphysical pain-related) emotional intensity and neural activity, and failed to observe activity in somatosensory regions (e.g., S2) (38, 39).

It is important to recognize that this is not the first study to demonstrate activation in S2 in the absence of a physical pain

stimulus. Research on empathy for pain indicates, for example, that under some circumstances the S2 becomes activated when individuals observe other people in physical pain (see refs. 40 and 41 for reviews). The current results differ from these findings by demonstrating that the S2 (as well as the dpINS) also respond to distress related to social-rejection when it is elicited intensely. An important question for future research is whether observing someone else experiencing intense social (rather than physical) pain (i.e., a parent witnessing their child's rejection) also recruits sensory-pain processing regions.

Before concluding, it is important to acknowledge that all of the participants in this study were trained on the Social Rejection and Physical Pain task before scanning and knew that they would be engaging in both tasks during the fMRI scan. Thus, it is possible that participants were primed to think about receiving physical pain on Social Rejection trials, which may have in turn played some role in accounting for the social rejection-related somatosensory activations that we observed. Three aspects of our design argue against this interpretation. First, participants were explicitly told that the Social Rejection and Physical Pain tasks would be administered separately, and they were informed during the scan when each task was about to begin and when each task was over. Second, the thermode was not placed on participants' forearms during the Social Rejection task, so they knew it was impossible for them to receive thermal stimulation on Social Rejection trials. Finally, participants were trained to relive their rejection experience on Social Rejection trials to powerfully manipulate social rejection and minimize the influence of task-irrelevant thoughts. Participants' ratings and postscan interviews suggested that they complied with these instructions. These caveats notwithstanding, research is needed to determine whether powerfully manipulating social rejection in the absence of any physical pain manipulations likewise recruits somatosensory activations. As research on this topic continues, it will likewise be important to examine whether having the expectation that one will be rejected in the future is capable of activating sensory pain regions, as physical pain expectancies have been shown to do (e.g., refs. 42 and 43).

Methods

Sample. Forty individuals (21 females) gave informed consent. All participants experienced an unwanted romantic relationship break-up within the past 6 months (M = 2.74 mo; SD = 1.70 mo), and indicated that thinking about their break-up experience led them to feel rejected; all participants scored above the midpoint on a 1 (not at all rejected) to 7 (very rejected) scale that asked them to rate how rejected they felt when they thought about their rejection experience (M = 5.60, SD = 1.06). Columbia University's Institutional Review Board approved the study.

Participants were recruited via flyers posted around Manhattan and advertisements posted on Facebook and Craig's List. The sample consisted of 60% Caucasian, 20% Asians, 10% African Americans, and 10% other. The mean age was 20.78 (SD = 2.59). All participants were right-handed native English language speakers and received $175 for their participation. Participants were screened to ensure that they did not suffer from any neurological or psychiatric illness, experience chronic pain, take psychoactive medications, antihistamine or steroids, have metal in their bodies, or have a history of substance use or abuse.

Design. See Fig. 1 for the design of the study.[†]

[†]Following this study, half the participants (n = 20) received a placebo manipulation and the other half did not (n = 20). All participants then engaged in the social rejection and physical pain tasks again. The results of this placebo manipulation on subsequent social rejection and physical pain-related neural activity are the focus of a subsequent article, and thus are not reported here. The between-subjects placebo vs. control manipulation was independent of all of the within-subjects effects that are the focus of the present article, and controlling for placebo vs. control manipulation at the group level did not qualitatively alter any of the results.

Social Pain Task Stimuli. The Social Rejection task was modeled after (*i*) fMRI research that used photographs provided by participants to elicit powerful emotions, including maternal love, romantic love, and rejection (8, 44–46), and (*ii*) behavioral research indicating that cueing people to recall autobiographical rejection experiences is an effective way of reactivating social rejection-related distress (e.g., refs. 36, 47, and 48). The stimuli for this task consisted of: (*i*) a headshot photograph of each participant's ex-partner and a same-gendered friend with whom they shared a positive experience around the time of their break-up (M = 2.46 mo; SD = 1.70 mo), and (*ii*) cue phrases appearing beneath each photograph that directed participants to focus on a specific experience they shared with each person. For additional details, see *SI Methods*.

Physical Pain Task Stimuli. The stimuli for the Physical Pain task consisted of thermal stimulations delivered to participants left volar forearm that participants judged to be nonpainful (level 2 on a 10-point scale) vs. near the limit of pain tolerance (level 8 on a 10-point scale). Following prior research (49–51), we used calibrated painful and nonpainful temperatures on a participant-by-participant basis to ensure that the subjective intensity of the stimuli was constant across participants. The temperature of these painful (i.e., Hot) and nonpainful (i.e., Warm) stimulations was determined via a pain-calibration task that took place before the experiment on the day of scanning. For details on physical pain calibration, see *SI Methods*.

Task Training. Before scanning, the experimenter walked participants through each step of the Social Rejection task (referred to as the "photograph" task to participants) and the Physical Pain task (referred to as the "heat" task to participants). They were told that that during the "photograph" task they would see the photographs of their ex-partner and friend. The experimenter explained that beneath each photograph, the cue-phrases they generated earlier would appear. When they saw each photograph they were asked to look directly at it and think about how they felt during the specific experience associated with the cue-phrase. Thus, when participants viewed the photograph of their ex-partner they were directed to think about how they felt during their break-up experience with that person; when they viewed the photograph of their friend they were directed to think about how they felt during their positive experience with that person. During the Physical Pain task, participants were instructed to focus on the fixation cross that appeared on the screen during the trials and think about the sensations they experienced as the thermode on their arm heated up. They were then instructed how to rate their affect after each type of trial and how to perform the visuospatial control task (see Fig. 1 for a description of these tasks and events).

Functional MRI Acquisition and Analysis. Whole-brain functional data were acquired on a GE 1.5 T scanner in 24 axial slices (3.5 × 3.5 × 4.5 mm voxels) parallel to the anterior commissure-posterior commissure (AC-PC) line with a T2*-weighted spiral in-out sequence developed by Dr. Gary Glover [repetition time (TR) = 2,000 ms, echo time (TE) = 40 ms, flip angle = 84, field of view (FOV) = 22 cm]. Structural data were acquired with a T1-weighted spoiled gradient-recalled sequence (1 × 1 × 1 mm; TR = 19 ms, TE = 5 ms, flip angle = 20).

Functional scans were preprocessed with SPM5, using slice-time correction, motion correction, spatial normalization to the MNI space, and spatial smoothing using a 6-mm full-width at half-maximum Gaussian kernel. Spatial normalization was performed by first coregistering the T1 spoiled gradient recalled (SPGR) to the mean functional image, normalizing the T1 to the SPM template using the "unified segmentation" algorithm applying the normalization parameters to the functional images, and sampling the resulting images at 3 × 3 × 3-mm resolution.

Statistical analyses were conducted using the general linear model framework implemented in Brain Voyager. Boxcar regressors, convolved with the canonical hemodynamic response function, modeled periods for the 15-s photo/heat period, 5-s affect rating, and 18-s visuospatial control task. The fixation-cross epoch was used as an implicit baseline. Voxelwise statistical parametric maps summarizing differences between trial types were calculated for each participant and then entered into random-effects group analyses, with statistical maps thresholded at $P < 0.05$ FWER-corrected for multiple comparisons across gray and white matter. This correction entailed a primary threshold of $P < 0.001$, with an extent threshold of 11 voxels, which was determined using a Monte Carlo simulation method, which was calculated using NeuroElf's (http://neuroelf.net/) instantiation of AlphaSim (52). This technique controls for the FWER by simulating null datasets with the same spatial autocorrelation found in the residual images and creates a frequency distribution of different cluster sizes. Clusters larger than the minimum size corresponding to the a priori chosen FWER are then retained for additional analysis. This cluster-based method of thresholding is often

more sensitive to activation when one can reasonably expect multiple contiguous activated voxels (52, 53), and is widely used in fMRI research.

Physical pain-processing localizer analysis. We localized pain-processing regions in a separate group of individual ($n = 75$) drawn from three separate thermal pain studies that contrasted high (level 8) vs. low (level 2) stimulation (Fig. S1). For additional details, see *SI Methods*.

Operculo-insular ROIs. We used the SPM Anatomy Toolbox (V1.6) to create ROIs bilaterally around the OP1 based on cytoarchitectonic mapping of the lateral operculum (54). We performed an ROI analysis on the dpINS bilaterally by building a 10-mm sphere around: (*i*) the peak dpINS coordinate (34, −14, 19) that evoked painful stimulation restricted to the upper limb in a direct electrical stimulation study of the insula (19); and (*ii*) the mirror site on the left hemisphere (−34, −14, 19). Monte Carlo simulations, calculated by using NeuroElf's instantiation of AlphaSim, indicated that a $P < 0.05$, 15-voxel minimum cluster size preserved an FWER $\alpha = 0.05$ threshold for both the OP1 and dpINS ROIs. One-tailed tests were used for these analyses because we had a priori hypotheses about activity increases with physical pain and social rejection.

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