HHS Public Access

Author manuscript

J Psychosom Res. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

J Psychosom Res. 2020 January ; 128: 109881. doi:10.1016/j.jpsychores.2019.109881.

When It Hurts Even More: The Neural Dynamics of Pain and Interpersonal Emotions

Alla Landa[1,2], **Brian A. Fallon**[1,2], **Zhishun Wang**[1,2], **Yunsuo Duan**[1,2], **Feng Liu**[1,2], **Tor D. Wager**[3], **Kevin Ochsner**[4], **Bradley S. Peterson**[5]

[1]Department of Psychiatry, Columbia University Medical Center, New York, NY

[2]New York State Psychiatric Institute, New York, NY

[3]Department of Psychological and Brain Sciences, Dartmouth College, Hanover, NH

[4]Department of Psychology, Columbia University, New York, NY

[5]Institute for the Developing Mind, Children's Hospital Los Angeles; Division of Child & Adolescent Psychiatry, Keck School of Medicine at USC, CA

Abstract

Objective: Chronic pain is highly prevalent among patients with mood, anxiety, personality, and somatic symptom disorders; and patients with chronic pain often suffer from persistent interpersonal distress. However, the neural mechanisms underlying this phenomenon and its possible role in the etiology of chronic pain are not yet understood. Based on our Developmental Theory of Centralized/Somatoform Pain, and prior research suggesting the existence of a shared neural system subserving interpersonal emotions and pain, we aimed to identify the neural basis for modulation of pain by feelings of interpersonal rejection and the role of the early interpersonal environment in development of this shared neural system.

Methods: During fMRI scanning, 22 healthy participants received moderately painful thermal stimuli in 3 interpersonal contexts: Acceptance, Rejection, and Reacceptance (modified Cyberball paradigm). Early interpersonal environment was assessed using the Parental Bonding Instrument.

Results: Interpersonal context modulated activity in pain neural systems during rejection and during accepting interactions with previously rejecting others. Moreover, the subjective perception of rejection, even when rejection was not occurring, correlated positively with reported pain severity and neural activity in the insula. The magnitude of neural modulation in pain circuits by feelings of rejection was associated with the quality of early interpersonal experience with caregivers.

Corresponding author: Alla Landa, Ph.D., Department of Psychiatry, Columbia University Medical Center, 1051 Riverside Drive, Unit 69, New York, NY 10032, Phone: 646-774-6717, AL2898@cumc.columbia.edu.

Declaration of interest: none

Conclusions: Results suggest that interpersonal emotions play an important role in the development and functioning of the pain system, supporting our Developmental Theory of predisposition to chronic centralized pain. These findings have direct implications for clinical practice, including the importance of treating interpersonal distress to alleviate pain.

Keywords

pain; interpersonal emotion; rejection; early interpersonal adversity; fMRI; psychosomatic medicine; developmental

INTRODUCTION

Chronic pain is the source of immense suffering and disability, affecting millions of people world-wide (1). It is highly comorbid with psychiatric disorders, being present in more than 50% of people who have depression or anxiety; and somatoform/centralized pain (bodily pain produced by nervous system without other medical causes) is a public health problem in many countries (2). Existing treatments are usually only partially effective. Chronic pain is a complex multifactorial phenomenon. Understanding the neural systems that produce, maintain, and modulate the experience of pain is of utmost importance for the development of more effective treatments for chronic pain.

We previously proposed a Developmental Theory for the pathogenesis and maintenance of centralized/somatoform pain. Evidence from diverse disciplines -- human and animal studies in developmental neuroscience, genetics, epigenetics, psychoneuroimmunology, cognitive affective neuroscience and clinical research (2) – suggests that shared genes, neurotransmitter systems, neural circuits, immunologic markers, and physiologic processes support both the experience of pain and feelings of interpersonal rejection or abandonment, and that early interaction with caregivers shapes its development and optimal maturation, which includes learning emotion-somatic distress differentiation and regulation (2, 3). Clinical research shows that chronic centralized pain is highly associated with hypersensitivity to interpersonal rejection (2, 4), sub-optimal childhood interpersonal environment (2, 5), and difficulty in awareness and expression of emotion to others (e.g., alexithymia) (2). Moreover, pain increases with interpersonal distress and exacerbated feelings of rejection (2, 6). Integrating these findings, our Developmental Theory suggests that non-optimal interpersonal environment in early life may disrupt the development of the shared neural system subserving interpersonal emotions and pain. It can hinder the development of the distress regulation and differentiation between affective and somatic aspects of distress, producing a vulnerability to developing rejection/abandonment hypersensitivity and chronic pain concurrently, and predispose a person to an impaired ability to differentiate and down-regulate the emotional distress associated with those experiences, all leading to a vicious cycle of increased feelings of rejection, loneliness, and pain.

Consistent with these prior clinical research findings, functional Magnetic Resonance Imaging (fMRI) studies have shown that parts of pain processing circuits are also involved in processing feelings of rejection elicited by a Cyberball paradigm (7) -- a computer task in

which a participant is first accepted into and then excluded from a ball-tossing game with two other cyber-participants (8). In another study, viewing a photograph of an ex-romantic partner following unwanted breakup activated distinct yet partially overlapping patterns of brain activity compared to processing thermal pain stimulation (9, 10). Administration of acetaminophen – a pain-relieving medication -- to healthy participants for 3 weeks significantly decreased feelings of rejection in response to Cyberball manipulation and was associated with decreased activation of the insula and anterior cingulate cortex (ACC) (11). These same regions have been implicated with the aberrant processing of pain (12–14) and gray matter loss (15) among patients suffering from centrally modulated chronic pain conditions (e.g. fibromyalgia, somatoform pain). A PET study of interpersonal exclusion using Cyberball showed that the availability of mu-opioid receptors correlated with self-reported feelings of rejection among heathy and depressed participants (16, 17). In addition, behavioral studies suggest that pain experience is affected by interpersonal context. For example, healthy participants reported increased pain when pain stimuli were administered in the context of rejection compared with the context of acceptance during Cyberball paradigm (18). In another study, pain stimuli perceived as delivered with malicious intent were experienced as more painful than stimuli perceived as delivered unintentionally (19).

Despite the progress made by prior imaging studies, the neural mechanisms by which feelings of interpersonal rejection modulate the experience of pain are unknown. Nor is it known to what extent the subjective *perception* of rejection modulates pain on a neural level, or whether interacting with others who were previously rejecting alters the experience of pain. Answers to these questions are important for understanding the neural basis of chronic pain among patients who persistently experience feelings of being lonely, rejected, hurt, or abandoned by others -- feelings that last beyond the actual moments of rejection. To study the neural mechanisms by which feelings of rejection modulate pain both during and after the rejection, we developed an fMRI paradigm in which sequences of moderately painful thermal stimuli were administered in the context of experimentally varied levels of interpersonal acceptance, rejection, and during a post-rejection, accepting interaction (“re-acceptance”). In the prior studies which suggested the overlap of pain and interpersonal emotion circuits, participants experienced somatic pain and feelings of interpersonal rejection separately; the conclusion about the overlap was based on the observation that some of the same neural circuits were implicated in both pain and feelings of rejection. The goal of the present study was to investigate *the interaction* of pain and interpersonal distress. We used fMRI to study neural activity underlying pain experienced in the context of ongoing interpersonal interaction (interpersonal acceptance, rejection, or reacceptance), as a step towards improving the ecologic validity of experimentally manipulated pain, as people usually experience pain in real life while interacting with others (family, coworkers, etc.).

Based on findings of prior imaging studies, we hypothesized that we would identify a significant interaction of pain with interpersonal context (rejection and re-acceptance compared with acceptance) in the ACC and insula. We also hypothesized, based on our Developmental Theory of Centralized/Somatoform Pain (2), that the strength of this modulation would be associated with non-optimal caregiving in childhood, as early interpersonal experiences shape development of this shared neural system and abilities for emotion-somatic distress differentiation, awareness, and regulation.

METHOD

Participants

Twenty-two healthy volunteers were recruited from the local community via flyers posted online. They were 22–48 years old (M= 31.4, SD= 8.1); 50% female; of diverse ethnicity (30% African American, 25% Asian, 25% Caucasian, 0% Hispanic) and education (13 to 19 years of education, M=15.7, SD=1.3). Excluded were participants with current psychiatric or medical disorder, pain symptoms or chronic pain, substance abuse, history of head injury, major neurologic or psychiatric conditions, or current use of psychotropic, pain or contraceptive medications. Eligibility was confirmed using the SCID (Structured Clinical Interview for DSMIV)(20) conducted by a PhD level psychologist, a physical exam conducted by a physician, basic clinical blood tests, and a urine toxicology screen. Female participants were scanned during the second half of the follicular phase of their menstrual cycle. FMRI data from two participants were excluded from analyses due to excessive head motion during scan.

We used the Parental Bonding Inventory (PBI) -- a retrospective self-report measure of fundamental parenting styles during one's childhood (<16yo) -- to assess the quality of early interpersonal environment (21). The PBI contains 25 statements about interactions with mother/father that participants rate on a 4-point Likert scale, ranging from "very like" to "very unlike," completed for mother and father separately. The scale is scored on two subscales: 'Care' and 'Overprotection/Control.' The care subscale includes 12 items, such as "Spoke to me in a warm and friendly voice" or reverse scored items such as "Made me feel I wasn't wanted." The Overprotection/Control subscale includes 13 items such as, "Tried to control everything I did" or reverse scored items such as "Liked me to make my own decisions." The combination of high Care and low Control/Overprotection comprises "optimal parenting" classification. The scale has good validity, reliability, and internal consistency (21, 22).

fMRI Paradigm

Calibration of Thermal Stimuli Prior to the fMRI Scan.—Prior to each fMRI scan, we conducted a calibration procedure to determine what temperature was moderately painful for each participant (rated as 5 on a 10-point visual analog scale (VAS)). Computer-controlled thermal stimuli were applied with a 16×16mm thermode (TSA-II; Medoc Advanced Medical Systems) to the distal lateral surface of the left forearm using a double random staircase algorithm, and participants rated each stimulus on a 10-point VAS. The temperature that elicited level 5 pain – subjectively a moderately painful temperature -- was used as pain stimulus #1 during the fMRI scan (labeled as "P1").

Pain Stimuli Used During the fMRI Scan.—The TSA-II device described above was also used to deliver temperature to the left arm during the scan. We used two types of pain stimuli: a) Pain Stimulus #1 (labeled "P1"), a temperature determined to elicit pain at level 5 for the participant prior to the scan; and b) Pain Stimulus #2 (labeled "P2"), the same temperature (42°C) delivered to all participants. Each thermal stimulus was delivered for 16

seconds and was followed by a pain rating on a 10-point VAS presented on the computer screen for 4 seconds.

Experimental Manipulation to Elicit Feelings of Rejection.—We used a well-validated experimental manipulation, Cyberball (7), to elicit feelings of interpersonal rejection, which we modified as described below. As in the original Cyberball, participants were told they would participate in a virtual ball-tossing game with two other people over the intranet (in reality a computer program). Each participant was first included in the game, and then excluded, when the other two players stopped throwing the ball to the participant while continuing to play between themselves. Our modifications of the original Cyberball (7) included: a) adding thermal pain stimulation throughout all interpersonal conditions, b) adding Re-Acceptance condition after Rejection to study whether the interaction of previously rejecting others affects pain experience, and c) extending the time of each interpersonal condition to accommodate pain stimuli and repetitions necessary for fMRI data acquisition. Participants were told that the purpose of the fMRI was to study the neural bases of pain during everyday life activities (e.g. interacting with others) simulated by playing a ball-tossing game.

fMRI Paradigm.—The paradigm consisted of 3 conditions/runs: (A) Acceptance -- each player had an equal chance of being thrown the ball from the other players; (B) Rejection – the other two players excluded the participant by throwing him/her the ball only 10% of the time, and (C) Re-Acceptance – the other two players resumed throwing the ball to the participant at the same frequency as during Acceptance. Because this order was needed to create the psychological effect of rejection and reacceptance, we did not counterbalance the conditions.

Each of the fMRI runs consisted of 11 Cyberball game segments (jittered between 20, 26, or 28 seconds each to avoid expectancy effects, with the same order of games within each run and across all participants), alternating with ten 16-second pain stimuli: 5 P1 stimuli (subjectively moderately painful temperature for each participant) and 5 P2 stimuli (standard stimuli of 42°C, same for all participants), presented in pseudo-random order within each run, with the order constant across the 3 runs and across the participants (Figure 1). Three-minute Arterial Spin Labeling (ASL) scans while playing Cyberball were acquired between BOLD runs (ASL data not presented here). After each run we prompted participants to rate on a 10-point VAS scale 10 statements, presented in a pseudo-random order, to assess how they felt at the moment in terms of any bodily pain other than pain from thermal stimulation, general negative/positive emotions (“I feel good”), feelings of rejection (e.g. “I feel rejected”), any physical discomfort of being in the scanner (“I feel comfortable”) and others. Questions pertaining to interpersonal rejection were purposefully imbedded in the longer list of other questions to prevent participants from guessing the research manipulation. During debriefing, participants were asked what had they thought was the purpose of the study; only 1 of 22 participants reported “wondering whether rejection was done on purpose.”

fMRI Data Acquisition and Preprocessing

Imaging data were obtained using a GE 3.0T scanner equipped with an 8-channel head coil and an echoplanar pulse sequence with TR=2000ms, TE=30ms, flip angle 77, field of view = 24, 3.5 mm slice thickness, no gap, 34 slices for whole brain coverage. Visual stimuli were programed in EPRIME and presented using a rear-projection screen and a mirror. Participants used a wireless mouse to play the Cyberball game and to rate pain and emotions on a VAS scale. See Supplementary Materials for details of image preprocessing.

fMRI Statistical Analysis

First Level Analysis.—We used the general linear model (GLM) in SPM8 for analyses of data at an individual participant level. First, we modeled BOLD signal for each participant using 6 independent functions in each run representing the canonical hemodynamic response function (HRF) convolved with a boxcar function (BCF) derived from the onsets and durations of (1) 5 P1 stimuli; (2) 5 P2 stimuli; (3) 5 Cyberball game segments preceding P1 stimuli; (4) 5 Cyberball segments preceding P2 stimuli; (5) times for the thermode to ramp up and reach the target temperature; and (6) rating of pain on the 10 VAS scale. We estimated the model using a restricted maximum likelihood (ReML) algorithm and modeled serial correlations with a first order autoregressive (AR(1)) model. For each run (acceptance, rejection, reacceptance) we contrasted the BOLD signal during P1 ratings with BOLD signal for Cyberball segments immediately prior to P1 stimuli. We then contrasted the resulting differences in BOLD signals between (1) Rejection and Acceptance, and (2) Re-Acceptance and Acceptance. The same analyses were performed for P2 stimuli.

Second Level Analysis.—We then applied a one-sample t-test to the contrast images generated at the first level and plotted beta values for BOLD signal in each condition of the contrast from the GLM during P1 stimuli and Cyberball to help determine the direction of the effects within the contrast. Statistical maps were thresholded using the conjoint requirement of $p < .01$ in a cluster of 28 contiguous voxels. The cluster size of 28 contiguous voxels was determined from a Monte Carlo simulation algorithm with 1000 iterations (a nonparametric approach to correcting for multiple comparisons that is less susceptible than parametric correction to false positive findings -- see Supplementary Materials.)

RESULTS

Behavioral Measures

Sensitivity to Thermal Pain During Calibration.—The average moderately painful temperature (VAS=5) before the fMRI scan was 42.4°C (SD=2.2), which on a group level did not differ significantly from the stimulus control temperature of 42.0°C (P2) (t=.86).

Experimental Manipulation of Feelings of Rejection.—As expected, participants reported that others were interacting with them significantly less during Rejection than during Acceptance and Re-Acceptance. During Rejection, compared to Acceptance, participants reported feeling significantly more excluded, rejected, and ignored (Figure 2, Table 1). Feelings of rejection persisted after the Rejection condition ended: participants

reported feeling significantly more excluded, rejected, and ignored during Re-Acceptance than during Acceptance (Figure 2, Table 1).

Pain Ratings During Interpersonal Interaction.—Average ratings of five subjectively moderately painful stimuli P1 and five P2 stimuli did not differ significantly between the interpersonal conditions (F=.14, ns and F=.59; ns). However, the pain rating of the first P1 stimulus in each run differed between interpersonal conditions: during Rejection it was on average significantly more painful than during Acceptance (t=−2.35 p=.03) (Table 1). Participants then rapidly habituated to pain stimuli during each run. The first stimulus (P1) in each run was rated significantly higher than the next four P1 stimuli in all conditions: Acceptance (t=−4.61, p<.001), Rejection (t= −6.1, p<.001), and ReAcceptance (t=−4.1, p=.001).

While participants reported feeling a gradual decline in the level of physical comfort and general valence of emotions (“feel good”) during our long scan (Figure 2), these variables did not follow the pattern of change in feelings of rejection between runs (Figure 2) and were not significant predictors of average P1 pain ratings in a linear regression, whereas “feeling rejected” significantly positively predicted average P1 ratings during Acceptance (β=.74, p=.003) and ReAcceptance (β=.68, p=.009).

Isolation of the Effect of *Perceived* Rejection on Pain Ratings.—The temperature that had been rated 5 on 10-point VAS during pre-fMRI calibration procedure (while participants were not playing Cyberball) was rated as less or more painful when participants experienced it while playing Cyberball-Acceptance game (ranging between 1.5 and 6.5, M=3.9, SD=1.66) – that is, interpersonal interaction affected the experience of pain.

Average P1 ratings during Acceptance correlated positively with reports of feeling excluded during that portion of the paradigm (r=.68, p=.001), when participants in fact were not excluded (they received the ball an equal percentage of time as the other two players). Their reported level of interaction with others, however, did not significantly correlate with P1 pain ratings. Therefore, if was rather *feeling* of rejection than misperception of the game that was associated with pain experience.

We then used linear regression to determine whether feelings of rejection and pain during ReAcceptance were more strongly predicted by participants *perceiving* others as rejecting (feeling rejected during Acceptance) or by reaction to the actual rejecting behavior of others (feeling rejected during Rejection). It was the perception of being rejected during Acceptance (β=.51, p=.03), rather than reaction to rejection during the Rejection condition (β=.10, ns), that contributed to feelings of rejection and to pain ratings (P1) during ReAcceptance (β=.55, p=.03 and β=−.09, ns. respectively).

Early Interpersonal Environment and Modulation of Pain by Feelings of Rejection.—Pain ratings and interpersonal feelings during Acceptance, Rejection, and ReAcceptance were significantly correlated with PBI scores. Lower level of reported Mother’s and Fathers’ Care and higher level of Mother’s and Fathers’ Control/ Overprotection were associated with stronger pain and stronger feelings of rejection, and

with feeling less liked (Table 2). Of note, feeling more rejected during Acceptance was significantly positively correlated with Mother's and Father's control/overprotection during childhood; feeling liked during Acceptance was negatively correlated with Mother's control/overprotection.

FMRI Findings (see more details in Supplementary Materials)

Modulation of BOLD Signal during Pain by Interpersonal Context—Rejection vs Acceptance: interpersonal context significantly modulated BOLD signal during administration of P1 pain stimuli in multiple regions: the limbic system (insula, hippocampus), putamen, pons, and temporal (MTG) and parietal cortices (Figures 3 and 5). P2 findings (not shown) were similar.

Rejection vs ReAcceptance: interpersonal context significantly modulated BOLD signal during administration of P1 pain stimuli in multiple regions: limbic system (right amygdala, vACC), pons, cerebellum, and temporal (MTG) and parietal cortices (Figure 4).

Feelings of Rejection and Non-Specific Negative Affect Differentially Modulate Pain Circuits—During Rejection, the reported level of "feeling excluded" correlated significantly with BOLD signal in the insula during pain stimulation and during the Cyberball game ($p<.025$), whereas "feeling good" significantly correlated with BOLD signal in the superior frontal gyrus during both activities ($p<.025$), suggesting that distinct neural circuits underlie feelings of rejection and general negative emotions (Figure 5A).

Effect of *Perceived* Interpersonal Rejection on Pain Circuits—During the Acceptance condition, when all players received the ball an equal number of times, some participants reported that they felt somewhat excluded (M=.78, SD=1.04; range 0–4 on a 10-point scale). The degree to which participants reported feeling excluded during Acceptance correlated significantly and positively with pain they experienced during P1 stimulation ($r=.48$, $p < .05$) and with BOLD signal change in the left insula ($p<.025$; Figure 5B).

Effect of Early Interpersonal Environment on Neural Modulation of Pain by Feelings of Interpersonal Rejection—To explore whether the degree of modulation of pain by rejection was associated with the reported quality of early relationships with caregivers, we assessed correlations of the contrasts presented in Figure 3 with scores on PBI subscales. The Mother's Care subscale correlated positively with strength of the pain-by-interpersonal context interaction in the insula, and negatively with the strength of pain-by-interpersonal context interaction in the rostral ACC and caudate, whereas Control/Overprotection correlated positively with the strength of pain-by-interpersonal context interaction in the rostral ACC (Figure 5C).

DISCUSSION

Our findings provide compelling preliminary evidence that feelings of interpersonal rejection modulate the neural processing of pain, supporting the study hypotheses. Moreover, the degree to which participants *perceived* others to be rejecting, regardless of whether the rejection occurred, correlated positively with reported pain intensity, as well as

with neural activity in pain processing systems. The intensity of pain experienced in interpersonal contexts was also associated with measures of the quality of early childhood caregiving, which in turn correlated with brain activity during pain and the strength of emotion-pain interaction on neural level, thereby supporting the mechanisms and theory of pathogenesis proposed in our Developmental Theory of Centralized/Somatoform Pain (2): non-optimal early interpersonal environment may affect the development of emotion differentiation and regulation potentially predisposing a person to experiencing emotional distress on a more somatic/bodily level.

Feelings of Interpersonal Rejection Modulate the Neural Processing of Pain

Pain experienced in all three interpersonal contexts activated brain regions (insula, ventral striatum, dACC, somatosensory cortex) previously reported as subserving the experience of pain (23, 24). Interpersonal rejection significantly modulated activity in multiple neural systems, including limbic and pain-processing regions (hippocampus, bilateral putamen, bilateral insula, and pons) (Figure 3). Insula activation during the experience of pain was on average greater during rejection than during acceptance, and it correlated with ratings of feeling rejected in the contexts of both rejection and acceptance, and with reported maternal care during childhood. These findings suggest that the insula may react specifically to interpersonal distress rather than to general negative emotions, as ratings of the overall valence of emotions (“feeling good”) during rejection correlated with activation of prefrontal cortex, but not insula.

The putamen activated significantly more during pain experienced in the context of interpersonal rejection than pain experienced during acceptance. This is the same region implicated in aberrant pain processing among patients with chronic pain (25). The putamen is also implicated in reward processing, stimulus-response learning (26), and the exchange of information between higher cortical and midbrain centers during experience of pain (27), suggesting that it can play a role in learning to associate interpersonal distress with physical pain. Dampened activation of the pons (which relays pain information between the brain and the body) during rejection suggests a potential mechanism whereby interpersonal rejection can alter somatic state.

Interpersonal rejection diminished activity in the superior frontal gyrus during pain processing. As superior frontal gyrus has been implicated in response inhibition, as well as executive functioning and self-awareness, our findings suggest that social rejection may attenuate the down-regulation of pain. Similarly, brain regions that subserve attention, reactivity to changes in environment, and sensory integration (PCC, IPL)(28–30) activated during pain stimulation in the context of interpersonal acceptance, but not to pain stimuli in the context of rejection; BOLD signal change in MTG - implicated in attention and goal directed behavior - decreased during rejection versus acceptance. Regions reported as activated in previous studies of pain, such as cuneus (31), precuneus (32), and post-central and precentral gyri, also activated in our study in response to pain, but during acceptance and not rejection, suggesting that interpersonal rejection may attenuate the cognitive and somatosensory processing of pain. Diminished activation in the lingual gurus -region implicated in processing of emotion words and emotional images (33, 34) – during rejection

compared with its activation during acceptance points to potential disruption of emotional processing and the discrimination of emotion from pain.

Overall, this pattern of modulation suggests that feelings of rejection disrupt the down-regulation of pain, as regions usually involved in the down regulation of limbic and pain circuits were less reactive to pain in the context of rejection compared with acceptance. We speculate that this neural modulation may derive from overlap of the neural systems that process pain and feelings of rejection. Feelings of rejection may compete with somatic pain for the same neural resources that down-regulate the intensity of painful experiences. Additionally, this pattern of findings suggests a potential loss of neural differentiation between emotion and somatic pain during feelings of interpersonal rejection. In fact, difficulty discriminating emotion from somatic pain is a common problem among patients suffering from chronic pain conditions(35), and it has been suggested as pathogenic in chronic centralized/somatoform pain (2). Moreover, the neural systems that subserved the modulation of pain by interpersonal rejection in our study were also implicated in the aberrant central processing of pain in patients with chronic pain (12, 14, 36).

Our findings also suggest that even after rejection ends, it continues to affect brain activity. Lingering feelings of rejection during interaction with previously rejecting others modulated neural activity during pain in multiple limbic and pain circuits (Figure 4). Heightened activation of the amygdala and pons, together with dampened activation of the parahippocampus, precentral gyrus, SMA, MTG, and precuneus, suggest that either the anticipation of perceived threat of renewed rejection or resentment over being recently rejected attenuate down-regulation of pain processing.

Pain can be modulated by positive and negative thoughts, emotions (37–40), and environmental factors (41). Our findings support the idea that feelings of interpersonal distress compared to general negative emotions may have a distinct neural representation (42, 43) and a distinct mechanism for modulating pain.

Perceived Rejection in the Neural Modulation of Pain

We explored individual differences in the extent to which interpersonal context modulated the experience of pain. First of all, once the temperature that had been pre-calibrated as moderately painful (rated 5 on 10 point VAS by a participant) was delivered during a simple interaction with others (Acceptance part of ball tossing game) it was rated as more painful by some participants and less painful by others. Moreover, the intensity of feeling rejected reported during the Acceptance condition correlated with those ratings of pain intensity and activation of the insula. A tendency to perceive others as rejecting may reflect an object relational representation of others, which is often associated with early interpersonal experience. In our study, perception of rejection and feeling less liked during acceptance was, in fact, significantly associated with the reported poorer quality of parental care during early childhood, supporting this hypothesis. Overall, these findings suggest that in addition to the feelings regarding actual rejection, feelings regarding *perceived* rejection play a role in the modulation of pain.

Additionally, reported feeling of *perceived rejection* (during Acceptance) but not *rejection feeling during actual rejection* (during Rejection) correlated significantly with both feeling rejected and the strength of pain experienced when interacting with previously rejecting others during ReAcceptance. These findings point to a basic mechanism underlying the effects of perceived rejection on pain processing. They may be particularly relevant for patients who have heightened rejection sensitivity and expectations that others will reject, hurt, or abandon them - a perception of others previously shown to be the dominant relational schema in 90% of patients with chronic somatoform pain compared with 10% of healthy controls (44). These findings may also help explain why 50–75% of patients with depression (45–48), 45% with anxiety, and up to 80% with borderline personality disorder suffer from chronic pain that is unexplained by another medical condition (49, 50). Brain imaging studies of feelings of rejection and pain interaction in clinical populations are needed to investigate these hypotheses further.

Childhood Parental Care Affects the Modulation of Pain by Feelings of Rejection

Neural dynamics of pain and feelings of rejection were associated with participants' self-reported quality of parental care during childhood. Poorer emotional care and increased overprotection/control by parents were associated with reports of more severe pain during rejection and a stronger interaction of pain with interpersonal context on neural level (Table 2, Figure 5), suggesting that people who grow up in such environments may be more susceptible to somatic pain when feeling lonely, hurt, or rejected. This finding is consistent with numerous reports of early life interpersonal adversity and environments that restrict emotional development in patients with chronic centralized/somatoform pain (2, 5) and with the possible mechanisms of pathogenesis proposed in the Developmental Theory of Centralized/Somatoform Pain (2), in turn, having direct implications for treatment. Of note, in our study, the effects of non-optimal early interpersonal environment on pain processing were evident in non-symptomatic individuals. This suggests that assessment of developmental factors, early interpersonal environment, and current interpersonal distress among patients who present with pain symptoms and no other reported psychosocial distress may be an important part of a clinical evaluation.

Study Limitations

Counter-balancing the order of conditions (acceptance, rejection, reacceptance) was not possible as the specific order was necessary to elicit the psychological effects of (a) feeling excluded (following prior inclusion) and (b) engaging in accepting interaction with previously rejecting others. Experiencing pain stimuli rated as moderate (VAS=5) in the context of interpersonal interaction led to increased variability in P1 ratings during acceptance, thereby creating subjectively different pain baselines (ranging from 1.5 to 6.5) for the Cyberball manipulation, and potentially weakening statistical effects by introducing an additional source of variability. Controlling for pain ratings, however, did not change activation findings substantially. The interaction of feelings of rejection and pain may be bidirectional. Our study design does not support inferences about unidirectional effects of causation. The sample size is relatively small, which may have led to some false negative results. The risk for false positive findings was addressed using a nonparametric approach to correction for multiple comparisons, which is less prone to false positives.

Conclusions

Overall, our findings provide preliminary evidence that feelings of interpersonal rejection amplify the experience of pain and dampen the top-down regulation of pain processing. Individual differences in feelings of interpersonal rejection -- whether elicited by actual behavior of others, expectation of rejection based on prior experience, or the subjective perception of being excluded in a non-excluding situation -increased activity in pain circuits and attenuated activity in circuits that regulate processing of pain and emotion. Individual differences in the degree of this neural modulation by feelings of interpersonal rejection were associated with the quality of parenting during childhood.

The results of the study support the Developmental Theory of susceptibility to chronic centralized pain (2) and have direct implications for understanding the crucial role of interpersonal emotions in the experience of pain. They suggest the importance of early interpersonal relationships in influencing the interaction between emotion and pain circuits, as well as learning emotion-somatic pain differentiation and regulation. Alleviating interpersonal distress and reducing the tendency to perceive others as rejecting, hurting, or abandoning may be important components in the treatment of acute and chronic pain conditions, and deserve further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to thank Avi Chandra, Fawad Vikari, Sam Barberi, and Satie Shova for assistance with data collection, and Pangwei Wang for technical help.

This work was supported by the National Institutes of Health (T32 NIMH Training Grant MH018264-29 and NIA K23-AG054735)

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HIGHLIGHTS

- Feelings of interpersonal rejection modulate neural processing of pain
- Interaction with previously rejecting others affects neural response to pain
- *Perceiving* others as rejecting during accepting interactions amplifies pain on neural level
- Feelings of rejection may underlie loss of emotion vs pain neural differentiation
- Neural modulation of pain by interpersonal emotion is associated with quality of early parental care

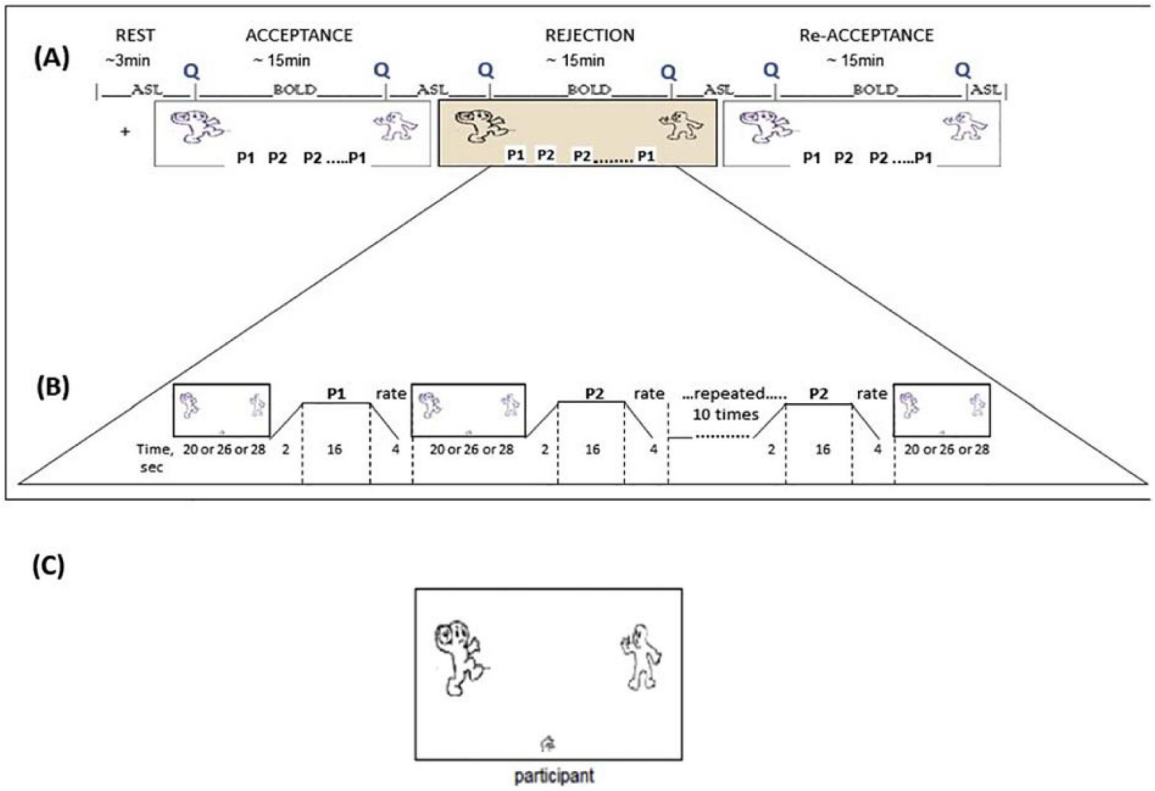

Figure 1. Design of the fMRI paradigm.

(A) Overall design of the paradigm, (B) Details of each run (BOLD= Blood oxygenation level dependent; ASL=Arterial Spin Labeling; P1= thermal stimulation using each participant's subjectively "moderately painful" temperature rated 5 on a 0–10 scale during calibration; P2=thermal stimulation using same temperature of 42°C for all participants); (C) Cyberball Game: in the center -participant's "hand"; the two cartoon figures represent other players; Q=set of questions about how the participant is feeing, rated on a 10 point scale

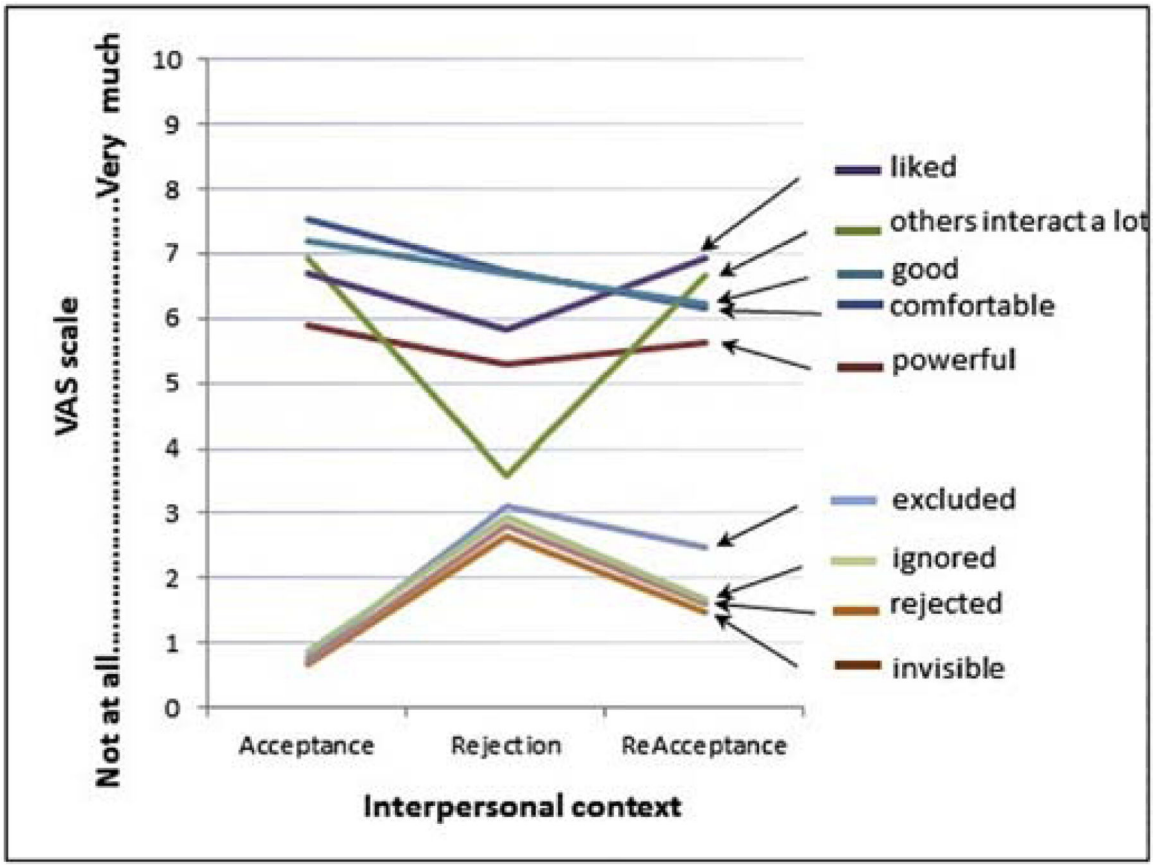

Figure 2.

Average self-reported feelings during three interpersonal conditions: Acceptance, Rejection, and ReAcceptance, rated on a 10-point visual analog scale (VAS).

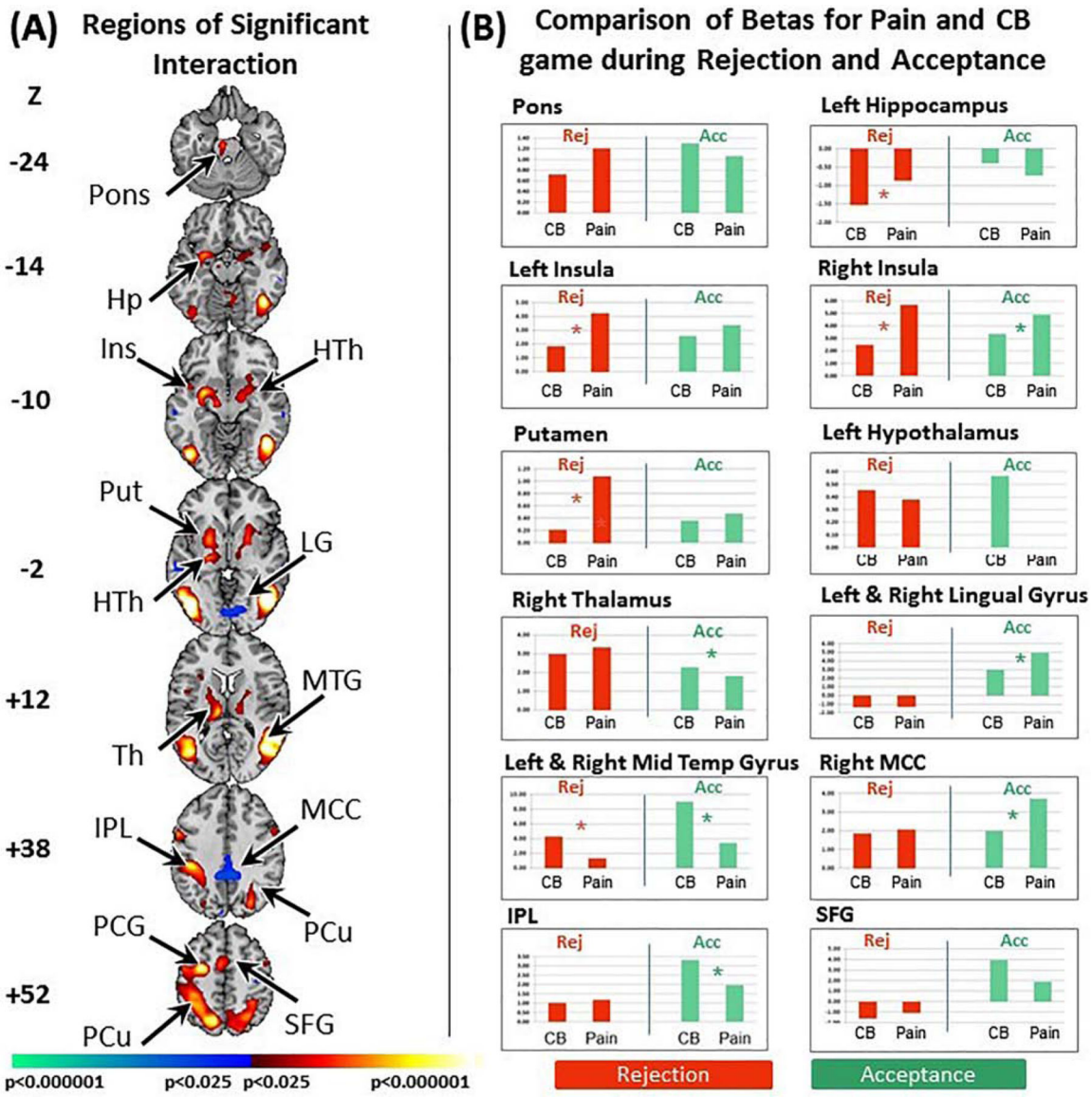

Figure 3. Modulation of Pain by Interpersonal Context: fMRI Signal for Pain during Rejection Compared with Acceptance

(A) Regions of statistically significant effect of pain (P1)-by-interpersonal rejection interaction on BOLD signal. Results suggest significant modulation of pain by context of rejection in multiple brain regions, including: Pons, hippocampus (Hp), hypothalamus (HTh), insula (Ins), putamen (Put), lingual gyrus (Lg), thalamus (Th), Medial Temporal Gyrus (MTG), Inferior parietal lobule (IPL), Mid Cingulate Cortex (MCC), Precuneus (PCu), precentral gyrus (PCG) and Superior Frontal Gyrus (SFG).

(B) Plots of betas in the regions of significant pain (P1)-by-interpersonal Rejection interaction. Shown are betas during pain stimulation (P1) and Cyberball games before pain stimulation during the Acceptance condition (in green) and Rejection condition (in red). (*) represents a significant difference in betas for P1 and Cyberball within a run.

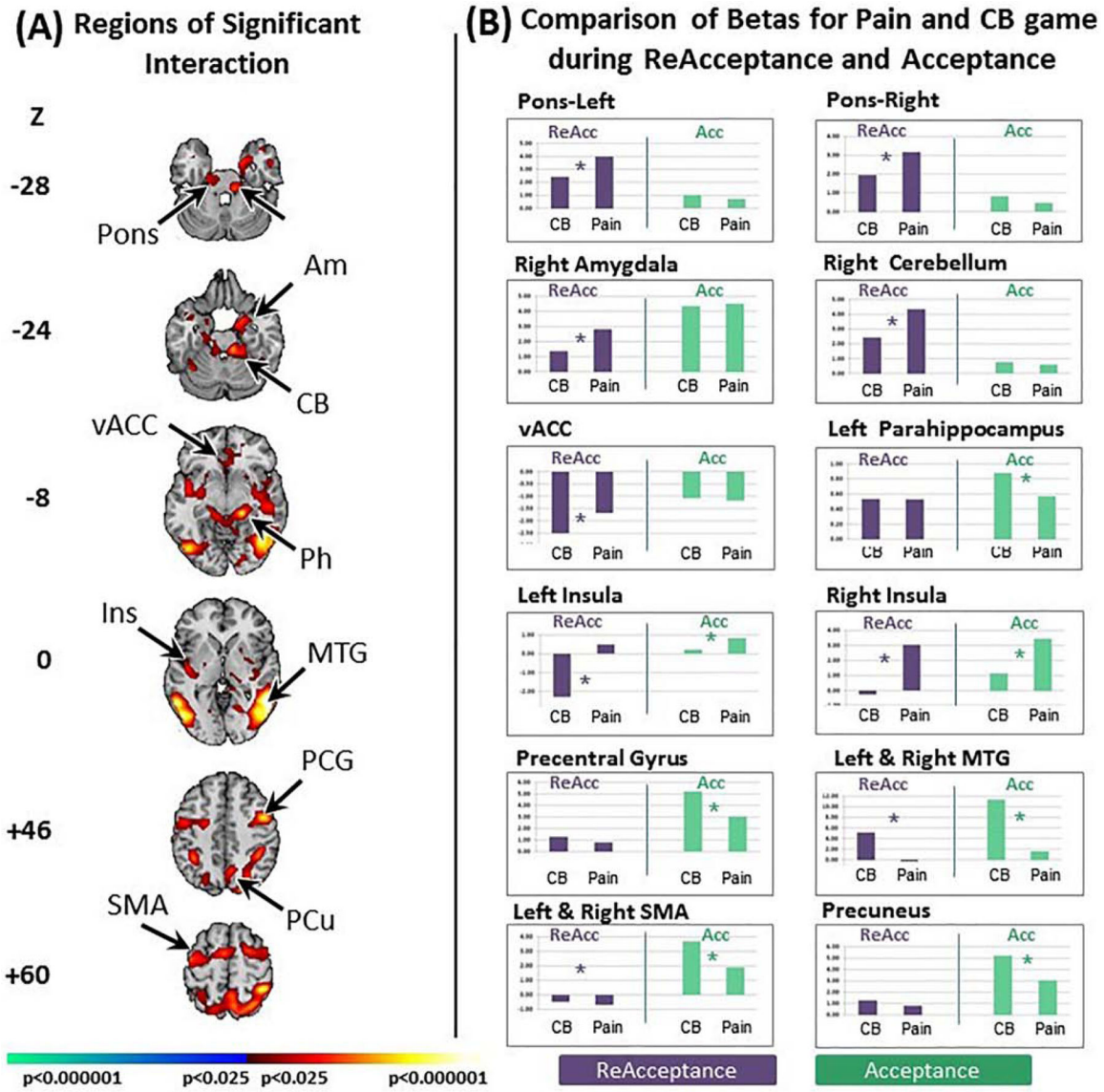

Figure 4. Modulation of Pain by Interpersonal Context: fMRI Signal for Pain during ReAcceptance Compared with Acceptance

(A) Regions of statistically significant effect of pain (P1)-by-interpersonal Re-Acceptance interaction on BOLD signal. Results suggest significant modulation of pain by the context of Re-Acceptance in multiple brain regions, including: pons, amygdala (Am), cerebellum (CB), ventral anterior cingulate cortex (vACC), parahippocampus (Ph), insula (Ins), medial temporal gyrus (MTG), precentral gyrus (PCG), precuneus (PCu), supplementary motor area (SMA), and superior frontal gyrus (SFG).

(B) Plots of betas in the regions of significant pain (P1)-by-interpersonal Re-Acceptance interaction. Shown are betas during pain stimulation (P1) and Cyberball games before pain stimulation during the Acceptance condition (in green) and during the Re-Acceptance condition (in purple). (*) represents a significant difference in betas for P1 and Cyberball within a run.

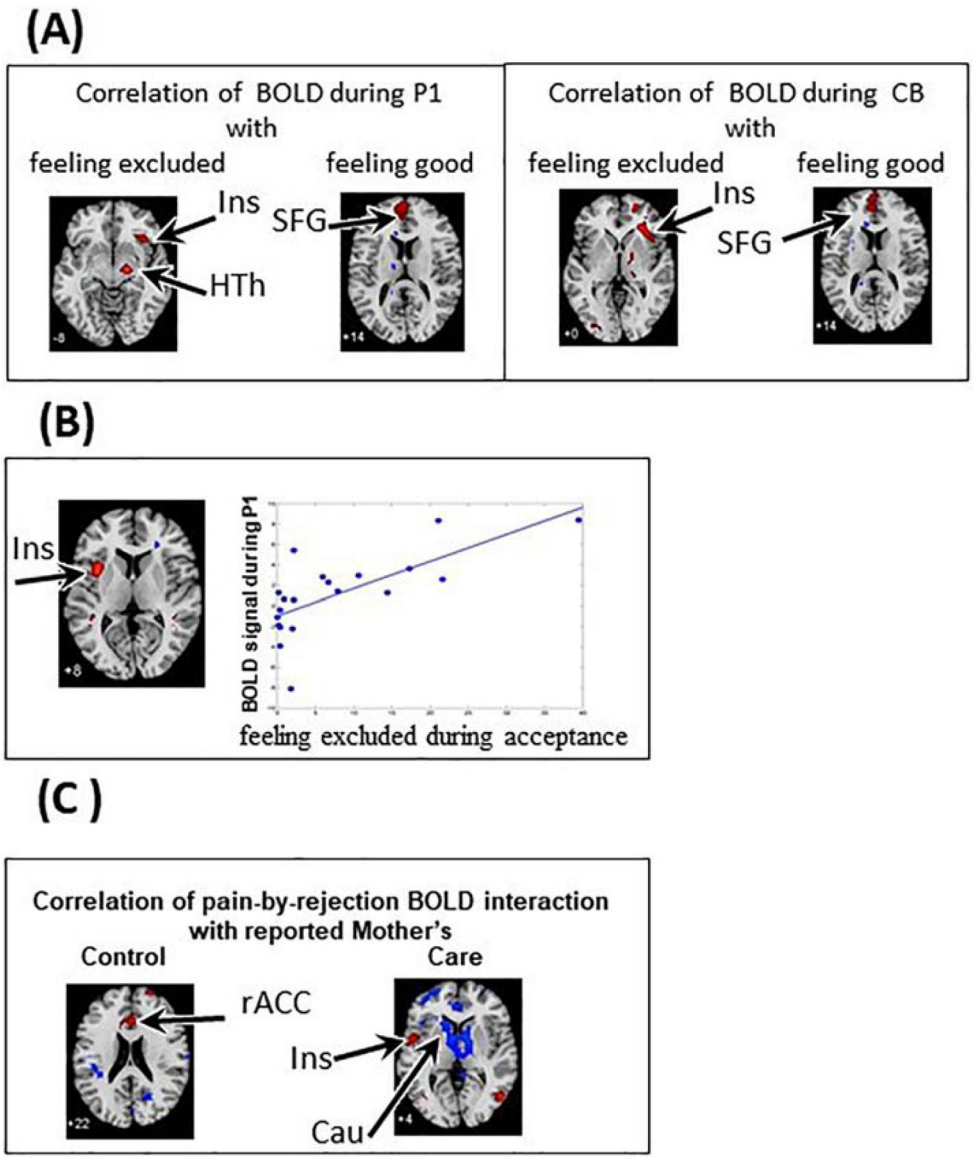

Figure 5.

(A) Regions of significant correlation of BOLD signal during pain stimulation (P1) and during Cyberball games segments (CB) with self-reported "feeling excluded" and "feeling good" during the Rejection run; Ins=insula; HTh= hypothalamus; SFG=superior frontal gyrus

(B) Region of significant correlation of BOLD signal in the left insula during pain stimulation (P1) with self-reported feeling excluded during the Acceptance condition (left). Graph representing the correlation of BOLD signal during P1 on the Y-axis with self-reported rating of feeling excluded during the Acceptance condition on the X axis (right).

(C) Regions of significant correlation between the strength of the pain-by-rejection interaction of BOLD signal (contrast in Figure 3) with the scores on PBI Mother's Control/ Overprotection (right) and Care (left) subscales; rACC=rostral anterior cingulate cortex; Ins=insula; Cau=Caudate.

Table 1.

Ratings of pain, emotion, and perception of others in varying interpersonal conditions

Self-report ratings during Scan	Interpersonal Context			Difference between Conditions			
	Acceptance	Rejection	Re-Acceptance	Acc. vs Rej.		Acc. vs Re-Acc.	
	M(SD)	M(SD)	M(SD)	t-test	p	t-test	p
Pain							
-subjectively moderate pain (avg for 5 P1 stimuli)	3.69 (1.66)	3.64 (1.71)	3.49 (1.75)	0.21	.84	0.53	.60
-stimulus control pain (avg for 5 P2 stimuli)	2.72 (1.87)	2.46 (1.63)	2.63 (1.87)	1.05	.31	0.22	.83
- 1st Pain Stimulus (PI) in run	5.29 (1.40)	6.15 (1.90)	5.25 (2.33)	−2.35	.03*	0.07	.95
Manipulation check							
-others interact with me a lot	7.43 (2.51)	3.90 (2.50)	6.77 (2.56)	5.82	.0002***	0.42	.68
Interpersonal emotions							
-feel excluded	0.78 (1.04)	3.11 (2.83)	2.47 (2.87)	−4.06	.001**	−2.70	.01*
-feel rejected	0.71 (0.87)	2.82 (2.75)	1.60 (1.85)	−3.68	.002**	−2.57	.02*
-feel ignored	0.87 (1.33)	2.96 (2.83)	1.67 (1.74)	−3.11	.006**	−1.93	.07
-feel invisible	0.70 (0.88)	2.66 (2.98)	1.47 (1.70)	−3.24	.005**	−2.70	.01*
-feel liked	6.69 (2.60)	5.81 (2.39)	6.91 (2.07)	1.84	.08	−0.66	.52
Non-specific emotions and comfort in the scanner:							
-feel good	7.53 (1.92)	6.85 (2.75)	6.28 (2.72)	2.06	.06	3.16	.005**
-feel comfortable	7.19 (2.34)	6.68 (2.69)	6.24 (2.76)	2.81	.01*	2.77	.01**
-feel powerful	5.98 (2.30)	5.29 (2.46)	5.63 (2.38)	1.92	.07	0.95	.36

* p<.05;

** p<.01;

*** p<.001

Table 2.

Correlations of Parental Bonding Instrument scores with pain and emotion ratings during Cyberball, and with pain sensitivity during calibration

Ratings of pain and of feelings during scan	Parental Bonding Instrument			
	Mother		Father	
	Care	Control/Overprotection	Care	Control/Overprotection
Interpersonal context				
None- calibration				
T° rated VAS=5	.06	.16	−.24	.34
Acceptance				
Pain Rating, PI	−.38*	.47*	−.19	.32
Rejected	−.30	.41*	−.19	.42*
Excluded	−.21	.27	−.07	.22
Liked	.19	−.45*	.02	−.32
Rejection				
Pain Rating, PI	−.30	.53**	−.40*	.46*
Rejected	−.27	.45*	−.42*	.61**
Excluded	−.33	.44*	−.36	.52**
Liked	.24	−.52**	.28	−.56**
ReAcceptance				
Pain Rating, PI	−.41*	.52**	−.43*	.45
Rejected	−.50*	.39*	−.11	.27
Excluded	−.60**	.44*	−.28	.26
Liked	.14	−.27	−.13	−.12

* p<.05;

** p<.01