



## When it hurts even more: The neural dynamics of pain and interpersonal emotions

Alla Landa<sup>a,b,\*</sup>, Brian A. Fallon<sup>a,b</sup>, Zhishun Wang<sup>a,b</sup>, Yunsuo Duan<sup>a,b</sup>, Feng Liu<sup>a,b</sup>, Tor D. Wager<sup>c</sup>, Kevin Ochsner<sup>d</sup>, Bradley S. Peterson<sup>e</sup>

<sup>a</sup> Department of Psychiatry, Columbia University Medical Center, New York, NY, United States of America

<sup>b</sup> New York State Psychiatric Institute, New York, NY, United States of America

<sup>c</sup> Department of Psychological and Brain Sciences, Dartmouth College, Hanover, NH, United States of America

<sup>d</sup> Department of Psychology, Columbia University, New York, NY, United States of America

<sup>e</sup> Institute for the Developing Mind, Children's Hospital Los Angeles, Division of Child & Adolescent Psychiatry, Keck School of Medicine at USC, CA, United States of America

### ARTICLE INFO

#### Keywords:

Pain  
Interpersonal emotion  
Rejection  
Early interpersonal adversity  
fMRI  
Psychosomatic medicine  
Developmental

### 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.

**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.

### 1. 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 [2]. 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

\* Corresponding author at: Department of Psychiatry, Columbia University Medical Center, 1051 Riverside Drive, Unit 69, New York, NY 10032, United States of America.

E-mail address: [AL2898@cumc.columbia.edu](mailto:AL2898@cumc.columbia.edu) (A. Landa).

<https://doi.org/10.1016/j.jpsychores.2019.109881>

Received 29 April 2019; Received in revised form 11 November 2019; Accepted 17 November 2019

0022-3999/ © 2019 Elsevier Inc. All rights reserved.

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 distress regulation as well as differentiation between affective and somatic aspects of distress, producing a vulnerability to developing rejection/abandonment hypersensitivity and somatic symptoms (e.g. chronic pain), and, therefore, 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 healthy 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 with others (“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 re-acceptance) as a step towards improving the ecological 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.

## 2. Method

### 2.1. 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 DSM-IV) [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 and 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].

### 2.2. fMRI Paradigm

#### 2.2.1. 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 16x16mm 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”).

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

### 2.2.3. 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.

### 2.2.4. fMRI paradigm design

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 s each to avoid expectancy effects, with the same order of games within each run and across all participants), alternating with ten 16-s 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 (Fig. 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.”

### 2.3. fMRI Data acquisition and preprocessing

Imaging data were obtained using a GE 3.0 T scanner equipped with an 8-channel head coil and an echoplanar pulse sequence with TR = 2000 ms, TE = 30 ms, 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.

### 2.4. fMRI Statistical analysis

#### 2.4.1. 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; (1) 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.

#### 2.4.2. 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.)

## 3. Results

### 3.1. Behavioral measures

#### 3.1.1. Sensitivity to thermal pain during calibration

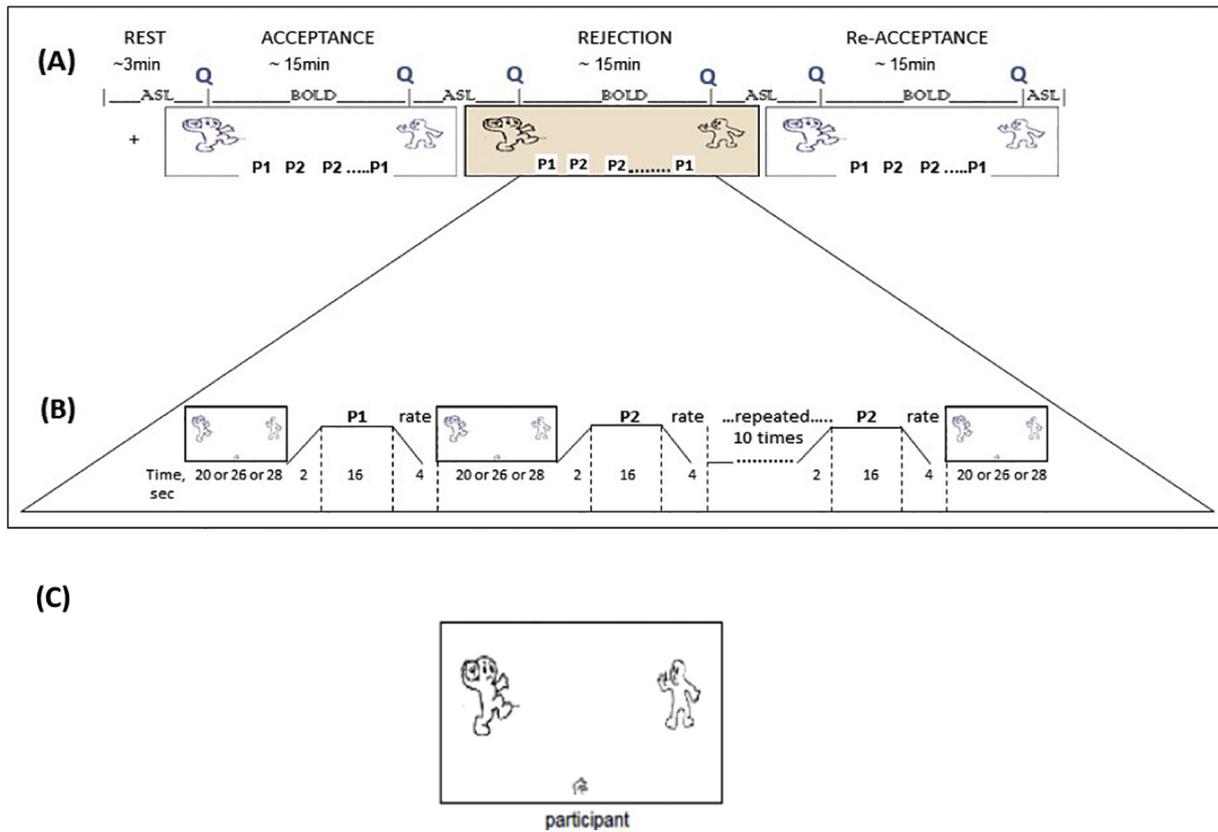
The average moderately painful temperature (VAS = 5) before the fMRI scan was 42.4°C (SD = 2.2), which on a group level did not differ significantly from the stimulus control temperature of 42.0°C (P2) ( $t = 0.86$ ).

#### 3.1.2. Experimental manipulation of feelings of rejection

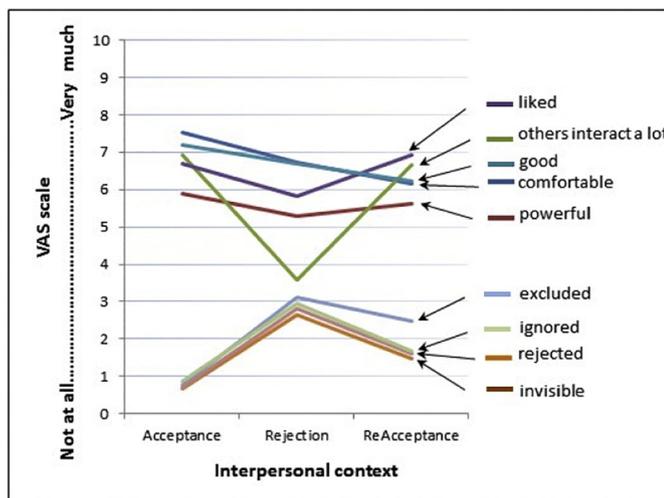
As expected, participants reported that others were interacting with them significantly less during *Rejection* than during *Acceptance* and *Re-Acceptance*. During *Rejection*, compared to *Acceptance*, participants reported feeling significantly more excluded, rejected, and ignored (Fig. 2, Table 1).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

#### 3.1.3. 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 ( $F = 0.14$ , ns and  $F = 0.59$ ; 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.



**Fig. 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 feeling, rated on a 10 point scale.



**Fig. 2.** Average self-reported feelings during three interpersonal conditions: Acceptance, Rejection, and ReAcceptance, rated on a 10-point visual analog scale (VAS).

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 (Fig. 2), these variables did not follow the pattern of change in feelings of rejection between runs (Fig. 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 ( $\beta = 0.74$ ,  $p = .003$ ) and ReAcceptance ( $\beta = 0.68$ ,  $p = .009$ ).

### 3.1.4. 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 ( $r = 0.68$ ,  $p = .001$ ), 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, it was rather the *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 Re-Acceptance 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 ( $\beta = 0.51$ ,  $p = .03$ ), rather than reaction to rejection during the Rejection condition ( $\beta = 0.10$ , ns), that contributed to feelings of rejection and to pain ratings (P1) during Re-Acceptance ( $\beta = 0.55$ ,  $p = .03$  and  $\beta = -0.09$ , ns, respectively).

**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
<b>Pain</b>							
Subjectively moderate pain (avg for 5 P1 stimuli)	3.69 (1.66)	3.64 (1.71)	3.49 (1.75)	0.21	0.84	0.53	0.60
Stimulus control pain (avg for 5 P2 stimuli)	2.72 (1.87)	2.46 (1.63)	2.63 (1.87)	1.05	0.31	0.22	0.83
1st Pain stimulus (P1) in run	5.29 (1.40)	6.15 (1.90)	5.25 (2.33)	-2.35	0.03*	0.07	0.95
<b>Manipulation check</b>							
Others interact with me a lot	7.43 (2.51)	3.90 (2.50)	6.77 (2.56)	5.82	0.0002***	0.42	0.68
<b>Interpersonal emotions</b>							
Feel excluded	0.78 (1.04)	3.11 (2.83)	2.47 (2.87)	-4.06	0.001**	-2.70	0.01*
Feel rejected	0.71 (0.87)	2.82 (2.75)	1.60 (1.85)	-3.68	0.002**	-2.57	0.02*
Feel ignored	0.87 (1.33)	2.96 (2.83)	1.67 (1.74)	-3.11	0.006**	-1.93	0.07
Feel invisible	0.70 (0.88)	2.66 (2.98)	1.47 (1.70)	-3.24	0.005**	-2.70	0.01*
Feel liked	6.69 (2.60)	5.81 (2.39)	6.91 (2.07)	1.84	0.08	-0.66	0.52
<b>Non-specific emotions and comfort in the scanner:</b>							
Feel good	7.53 (1.92)	6.85 (2.75)	6.28 (2.72)	2.06	0.06	3.16	0.005**
Feel comfortable	7.19 (2.34)	6.68 (2.69)	6.24 (2.76)	2.81	0.01*	2.77	0.01**
Feel powerful	5.98 (2.30)	5.29 (2.46)	5.63 (2.38)	1.92	0.07	0.95	0.36

\* p < .05.  
\*\* p < .01.  
\*\*\* p < .001.

**3.1.5. Early interpersonal environment and modulation of pain by feelings of rejection**

Pain ratings and interpersonal feelings during Acceptance, Rejection, and Re-Acceptance 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

**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 in various interpersonal contexts during scan	Parental Bonding Instrument (PBI)			
	Mother		Father	
	Care	Control/overprotection	Care	Control/overprotection
<b>None (calibration)</b>				
T <sup>o</sup> rated VAS = 5	0.06	0.16	-0.24	0.34
<b>Acceptance</b>				
Pain rating, P1	-0.38*	0.47*	-0.19	0.32
Rejected	-0.30	0.41*	-0.19	0.42*
Excluded	-0.21	0.27	-0.07	0.22
Liked	0.19	-0.45*	0.02	-0.32
<b>Rejection</b>				
Pain rating, P1	-0.30	0.53**	-0.40*	0.46*
Rejected	-0.27	0.45*	-0.42*	0.61**
Excluded	-0.33	0.44*	-0.36	0.52**
Liked	0.24	-0.52**	0.28	-0.56**
<b>Re-Acceptance</b>				
Pain rating, P1	-0.41*	0.52**	-0.43*	0.45
Rejected	-0.50*	0.39*	-0.11	0.27
Excluded	-0.60**	0.44*	-0.28	0.26
Liked	0.14	-0.27	-0.13	-0.12

\* p < .05.  
\*\* p < .01.

control/overprotection during childhood; feeling liked during Acceptance was negatively correlated with Mother's control/overprotection.

**3.2. fMRI findings**

**3.2.1. Modulation of BOLD signal during pain by interpersonal context**

**3.2.1.1. 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 (Figs. 3 and 5). P2 findings (not shown) were similar.

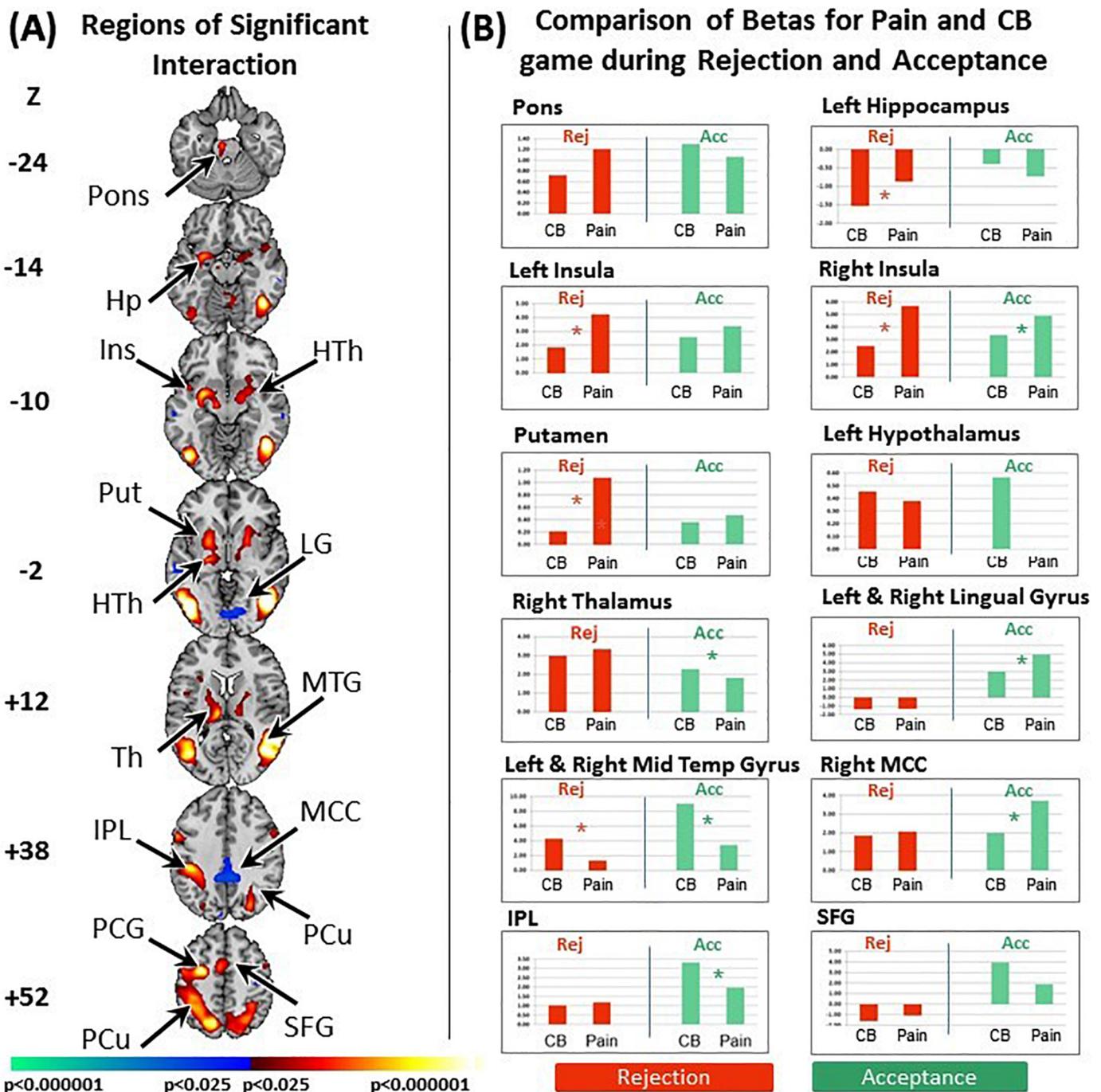
**3.2.1.2. Rejection vs ReAcceptance.** Interpersonal context significantly modulated BOLD signal during administration of P1 pain stimuli in multiple regions: limbic system (right amygdala, vACC), pons, cerebellum, and temporal (MTG) and parietal cortices (Fig. 4).

**3.2.2. Feelings of interpersonal 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 (Fig. 5A).

**3.2.3. 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 = 0.78, 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 = 0.48, p < .05) and with BOLD signal change in the left insula (p < .025; Fig. 5B).

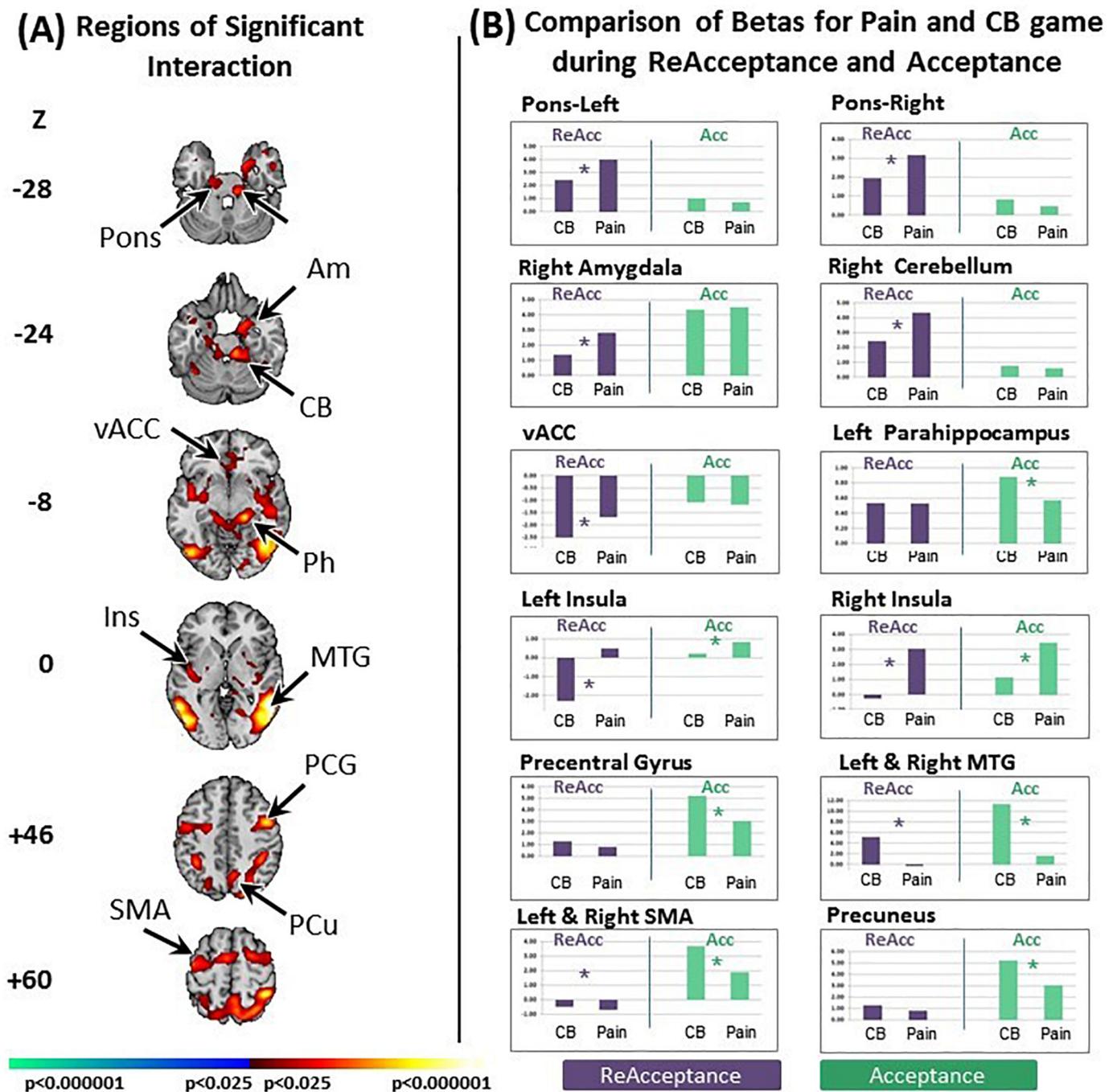


**Fig. 3.** Modulation of pain by interpersonal context: fMRI signal for pain during Rejection compared with Acceptance. (A) Regions of statistically significant effect of pain (P1)-by-interpersonal rejection interaction on BOLD signal. Results suggest significant modulation of pain by context of rejection 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 vingulate 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.

**3.2.4. 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 Fig. 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 (Fig. 5C).

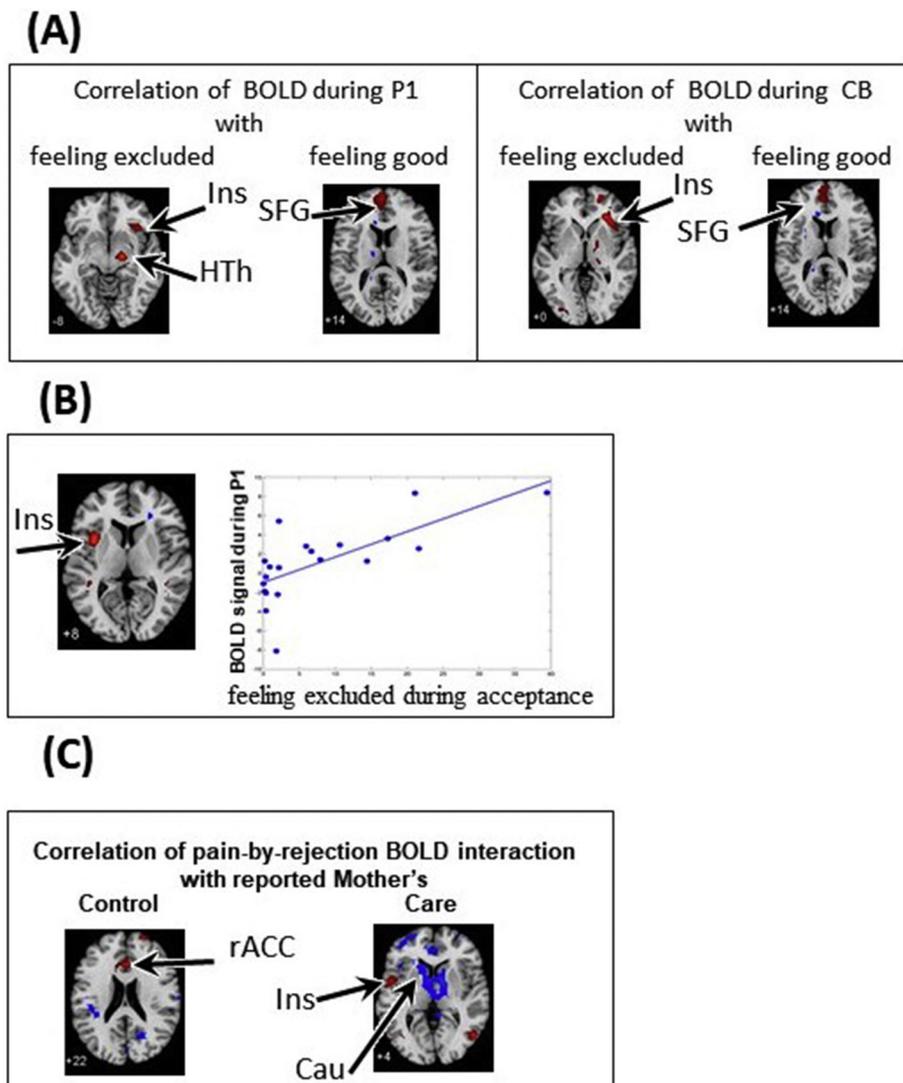


**Fig. 4.** Modulation of Pain by Interpersonal Context: fMRI Signal for Pain during ReAcceptance Compared with Acceptance. (A) Regions of statistically significant effect of pain (P1)-by-interpersonal Re-Acceptance interaction on BOLD signal. Results suggest significant modulation of pain by the context 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.

**4. 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



**Fig. 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 Fig. 3) with the scores on PBI Mother's Control/Overprotection (right) and Care (left) subscales; rACC = rostral anterior cingulate cortex; Ins = insula; Cau = caudate.

distress on a more somatic/bodily level.

#### 4.1. 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) (Fig. 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 gyrus - 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 (Fig. 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.

#### 4.2. 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 feelings of *perceived rejection* (during Acceptance) but not *rejection feelings 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 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.

#### 4.3. 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, Fig. 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.

#### 4.4. 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.

#### 4.5. 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.

## Declaration of Competing Interest

None.

## 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).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpsychores.2019.109881>.

## References

- [1] Institute of Medicine, *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, The National Academies Press, Washington, DC, 2011.
- [2] A. Landa, B.S. Peterson, B.A. Fallon, Somatoform pain: a developmental theory and translational research review, *Psychosom. Med.* 74 (2012) 717.
- [3] N.I. Eisenberger, M.D. Lieberman, Why rejection hurts: a common neural alarm system for physical and social pain, *Trends Cogn. Sci.* 8 (2004) 294–300.
- [4] A. Ehnavall, P. Mitchell, D. Hadzi-Pavlovic, G. Malhi, G. Parker, Pain during depression and relationship to rejection sensitivity, *Acta Psychiatr. Scand.* 119 (2009) 375–382.
- [5] B.A. Arnov, Relationships between childhood maltreatment, adult health and psychiatric outcomes, and medical utilization, *J Clin Psychiatry.* 65 (Suppl. 12) (2004) 10–15.
- [6] J.P. Blaustein, Knowing the unspeakable: Affectivity, object relatedness and the processes of somatization in individuals suffering with chronic somatic distress, *Dissertation Abstracts International: Section B: The Sciences and Engineering*, vol.62(63-B), 2001 (Sep 2001, pp).
- [7] K.D. Williams, B. Jarvis, Cyberball: a program for use in research on interpersonal ostracism and acceptance, *Behav. Res. Methods* 38 (2006) 174–180.
- [8] N.I. Eisenberger, M.D. Lieberman, K.D. Williams, Does rejection hurt? An fMRI study of social exclusion, *Science* 302 (2003) 290–292.
- [9] E. Kross, M.G. Berman, W. Mischel, E.E. Smith, T.D. Wager, Social rejection shares somatosensory representations with physical pain, *Proc. Natl. Acad. Sci.* 108 (2011) 6270–6275.
- [10] C.-W. Woo, L. Koban, E. Kross, M.A. Lindquist, M.T. Banich, L. Ruzic, J.R. Andrews-Hanna, T.D. Wager, Separate neural representations for physical pain and social rejection, *Nat. Commun.* 5 (2014).
- [11] C.N. DeWall, G. MacDonald, G.D. Webster, C.L. Masten, R.F. Baumeister, C. Powell, D. Combs, D.R. Schurtz, T.F. Stillman, D.M. Tice, Acetaminophen reduces social pain behavioral and neural evidence, *Psychol. Sci.* 21 (2010).
- [12] H. Gündel, M. Valet, C. Sorg, D. Huber, C. Zimmer, T. Sprenger, T. Tölle, Altered cerebral response to noxious heat stimulation in patients with somatoform pain disorder, *Pain* 137 (2008) 413–421.
- [13] M. Browning, P. Fletcher, M. Sharpe, Can neuroimaging help us to understand and classify somatoform disorders? A systematic and critical review, *Psychosom. Med.* 73 (2011) 173.
- [14] R.H. Gracely, F. Petzke, J.M. Wolf, D.J. Clauw, Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia, *Arthritis Rheum.* 46 (2002) 1333–1343.
- [15] M. Valet, H. Gündel, T. Sprenger, C. Sorg, M. Muhlau, C. Zimmer, P. Henningsen, T.R. Tolle, Patients with pain disorder show gray-matter loss in pain-processing structures: a voxel-based morphometric study, *Psychosom. Med.* 71 (2009) 49–56.
- [16] D.T. Hsu, B.J. Sanford, K.K. Meyers, T.M. Love, K.E. Hazlett, H. Wang, L. Ni, S.J. Walker, B.J. Mickey, S.T. Korycinski, R.A. Koeppel, J.K. Crocker, S.A. Langenecker, J.-K. Zubieta, Response of the  $\mu$ -opioid system to social rejection and acceptance, *Mol. Psychiatry* 18 (2013), <https://doi.org/10.1038/mp.2013.1096>.
- [17] D.T. Hsu, B.J. Sanford, K.K. Meyers, T.M. Love, K.E. Hazlett, S.J. Walker, B.J. Mickey, R.A. Koeppel, S.A. Langenecker, J.K. Zubieta, It still hurts: altered endogenous opioid activity in the brain during social rejection and acceptance in major depressive disorder, *Mol. Psychiatry* 20 (2015) 193–200.
- [18] N.I. Eisenberger, J.M. Jarcho, M.D. Lieberman, B.D. Naliboff, An experimental study of shared sensitivity to physical pain and social rejection, *Pain* 126 (2006) 132–138.
- [19] K. Gray, D.M. Wegner, The sting of intentional pain, *Psychol. Sci.* 19 (2008) 1260–1262.
- [20] M. First, R. Spitzer, M. Gibbon, W. JJPe, version. Structured clinical interview for Axis I DSM-IV disorders (SCID), (1994), p. 2.
- [21] G. Parker, H. Tupling, L.B. Brown, A parental bonding instrument, *Br. J. Med. Psychol.* 52 (1979) 1–10.
- [22] K. Wilhelm, G. Parker, Reliability of the parental bonding instrument and intimate bond measure scales, *Aust. N. Z. J. Psychiatr.* 24 (1990) 199–202.
- [23] T.D. Wager, L.Y. Atlas, M.A. Lindquist, M. Roy, C.-W. Woo, E. Kross, An fMRI-based neurologic signature of physical pain, *N. Engl. J. Med.* 368 (2013) 1388–1397.
- [24] A.V. Apkarian, M.C. Bushnell, R.D. Treede, J.K. Zubieta, Human brain mechanisms of pain perception and regulation in health and disease, *Eur. J. Pain* 9 (2005) 463–484.
- [25] P. Stoeter, T. Bauermann, R. Nickel, L. Corluka, J. Gawehn, G. Vucurevic, G. Vossel, U. Egle, Cerebral activation in patients with somatoform pain disorder exposed to pain and stress: an fMRI study, *Neuroimage* 36 (2007) 418–430.
- [26] J.A. Grahn, J.A. Parkinson, A.M. Owen, The cognitive functions of the caudate nucleus, *Prog. Neurobiol.* 86 (2008) 141–155.
- [27] C.J. Starr, L. Sawaki, G.F. Wittenberg, J.H. Burdette, Y. Oshiro, A.S. Quevedo, J.G. McHaffie, R.C. Coghill, The contribution of the putamen to sensory aspects of pain: insights from structural connectivity and brain lesions, *Brain* 134 (2011) 1987–2004.
- [28] T.D. Wager, J. Jonides, S. Reading, Neuroimaging studies of shifting attention: a meta-analysis, *Neuroimage* 22 (2004) 1679–1693.
- [29] R. Leech, D.J. Sharp, The role of the posterior cingulate cortex in cognition and disease, *Brain* 137 (2014) 12–32.
- [30] M. Corbetta, G.L. Shulman, Control of goal-directed and stimulus-driven attention in the brain, *Nat. Rev. Neurosci.* 3 (2002) 201–215.
- [31] R.K. Fulbright, C.J. Troche, P. Skudlarski, J.C. Gore, B.E. Wexler, Functional MR imaging of regional brain activation associated with the affective experience of pain, *Am. J. Roentgenol.* 177 (2001) 1205–1210.
- [32] P. Goffaux, L. Girard-Tremblay, S. Marchand, K. Daigle, K. Whittingstall, Individual differences in pain sensitivity vary as a function of precuneus reactivity, *Brain Topogr.* 27 (2014) 366–374.
- [33] N. Isenberg, D. Silbersweig, A. Engelien, S. Emmerich, K. Malavade, B. Ba, A. Leon, E. Stern, Linguistic threat activates the human amygdala, *Proc. Natl. Acad. Sci.* 96 (1999) 10456–10459.
- [34] E.G. Kehoe, J.M. Toomey, J.H. Balsters, A.L. Bokde, Healthy aging is associated with increased neural processing of positive valence but attenuated processing of emotional arousal: an fMRI study, *Neurobiol. Aging* 34 (2013) 809–821.
- [35] R.D. Lane, S.R. Waldstein, H.D. Critchley, S.W. Derbyshire, D.A. Drossman, T.D. Wager, N. Schneiderman, M.A. Chesney, J.R. Jennings, W.R. Lavallo, R.M. Rose, J.F. Thayer, O.G. Cameron, The rebirth of neuroscience in psychosomatic medicine, part II: clinical applications and implications for research, *Psychosom. Med.* 71 (2009) 135–151.
- [36] T. Giesecke, R.H. Gracely, M.A. Grant, A. Nchemson, F. Petzke, D.A. Williams, D.J. Clauw, Evidence of augmented central pain processing in idiopathic chronic low back pain, *Arthritis Rheum.* 50 (2004) 613–623.
- [37] M. Roy, M. Piché, J.-I. Chen, I. Peretz, P. Rainville, Cerebral and spinal modulation of pain by emotions, *Proc. Natl. Acad. Sci.* 106 (2009) 20900–20905.
- [38] K. Wiech, I. Tracey, The influence of negative emotions on pain: behavioral effects and neural mechanisms, *Neuroimage* 47 (2009) 987–994.
- [39] J.L. Rhudy, M.W. Meagher, The role of emotion in pain modulation, *Curr. Opin. Psychiatr.* 14 (2001) 241–245.
- [40] M.C. Bushnell, M. Čeko, L.A. Low, Cognitive and emotional control of pain and its disruption in chronic pain, *Nat. Rev. Neurosci.* 14 (2013) 502–511.
- [41] K. Wiech, M. Ploner, I. Tracey, Neurocognitive aspects of pain perception, *Trends Cogn. Sci.* 12 (2008) 306–313.
- [42] E. Kross, T. Egner, K. Ochsner, J. Hirsch, G. Downey, Neural dynamics of rejection sensitivity, *J. Cogn. Neurosci.* 19 (2007) 945–956.
- [43] A. Landa, Z. Wang, J.A. Russell, J. Posner, Y. Duan, A. Kangarlu, Y. Huo, B.A. Fallon, B.S. Peterson, Distinct neural circuits subserve interpersonal and non-interpersonal emotions, *Soc. Neurosci.* 8 (2013) 474–488.
- [44] A. Landa, A. Bossis, L. Boylan, P. Wong, Beyond the unexplainable pain: relational world of patients with somatization syndromes, *J. Nerv. Ment. Dis.* 200 (2012) 413–422.
- [45] M.J. Bair, R.L. Robinson, W. Katon, K. Kroenke, Depression and pain comorbidity: a literature review, *Arch. Intern. Med.* 163 (2003) 2433–2445.
- [46] B.A. Arnov, E.M. Hunkeler, C.M. Blasey, J. Lee, M.J. Constantino, B. Fireman, H.C. Kraemer, R. Dea, R. Robinson, C. Hayward, Comorbid depression, chronic pain, and disability in primary care, *Psychosom. Med.* 68 (2006) 262–268.
- [47] A. Garcia-Cebrian, P. Gandhi, K. Demyttenaere, R. Peveler, The association of depression and painful physical symptoms—a review of the European literature, *Eur. Psychiatr.* 21 (2006) 379–388.
- [48] K. Demyttenaere, C. Reed, D. Quail, M. Bauer, N. Dantchev, A.L. Montejo, B. Monz, D. Perahia, A. Tylee, L. Grassi, Presence and predictors of pain in depression: results from the FINDER study, *J. Affect. Disord.* 125 (2010) 53–60.
- [49] K. Demyttenaere, A. Bonnewyn, R. Bruffaerts, R. De Graaf, J.M. Haro, J. Alonso, Comorbid painful physical symptoms and anxiety: prevalence, work loss and help-seeking, *J. Affect. Disord.* 109 (2008) 264–272.
- [50] R.S. Biskin, F.R. Frankenburg, G.M. Fitzmaurice, M.C. Zanarini, Pain in patients with borderline personality disorder, *Personal. Ment. Health* 8 (2014) 218–227.