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Rejection Distress Suppresses Medial Prefrontal Cortex in Borderline Personality Disorder

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ABSTRACT

BACKGROUND: Borderline personality disorder (BPD) is characterized by an elevated distress response to social exclusion (i.e., rejection distress), the neural mechanisms of which remain unclear. Functional magnetic resonance imaging studies of social exclusion have relied on the classic version of the Cyberball task, which is not optimized for functional magnetic resonance imaging. Our goal was to clarify the neural substrates of rejection distress in BPD using a modified version of Cyberball, which allowed us to dissociate the neural response to exclusion events from its modulation by exclusionary context.

METHODS: Twenty-three women with BPD and 22 healthy control participants completed a novel functional magnetic resonance imaging modification of Cyberball with 5 runs of varying exclusion probability and rated their rejection distress after each run. We tested group differences in the whole-brain response to exclusion events and in the parametric modulation of that response by rejection distress using mass univariate analysis.

RESULTS: Although rejection distress was higher in participants with BPD ($F_{1,40} = 5.25$, $p = .027$, $\eta^2 = 0.12$), both groups showed similar neural responses to exclusion events. However, as rejection distress increased, the rostromedial prefrontal cortex response to exclusion events decreased in the BPD group but not in control participants. Stronger modulation of the rostromedial prefrontal cortex response by rejection distress was associated with higher trait rejection expectation, $r = -0.30$, $p = .050$.

CONCLUSIONS: Heightened rejection distress in BPD might stem from a failure to maintain or upregulate the activity of the rostromedial prefrontal cortex, a key node of the mentalization network. Inverse coupling between rejection distress and mentalization-related brain activity might contribute to heightened rejection expectation in BPD.

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Maslow's Theory of the Hierarchy of Needs (1) describes the 4 fundamental social needs that motivate human behavior: belonging, self-esteem, control, and meaningful existence (2–5). Social exclusion is a direct threat to these needs, often leading to rejection distress, the negative affective response to perceived social exclusion. Rejection distress is a cardinal symptom of borderline personality disorder (BPD) (6–10) and a core trait that distinguishes BPD from related personality and mood disorders (7,9,11–14). In people with BPD, social exclusion can prompt emotionally distressing experiences (8,9) that often lead to high-risk urges and behaviors, including self-harm, suicide attempts, and suicide completions (15), that can erode the individual's sense of belonging and connection to loved ones and significant others. Rejection distress–related interpersonal disturbances can also reinforce the other core symptoms of BPD in a vicious spiral.

The Cyberball game (16), an interactive ball-tossing game that experimentally manipulates social exclusion, is a widely used laboratory paradigm for studying the effects of social exclusion on behavior and brain activity. The game consists of a participant virtually throwing and catching a ball with 2 other computer-controlled players. Typically, one run of the game consists of equal or fair inclusion (i.e., 50% probability that a computer player throws the ball to the participant) and a second run that starts with equal probability of inclusion but, halfway through the run, transforms into complete exclusion of the participant. Although multiple neuroimaging studies have used Cyberball to identify the neural substrates of social exclusion in both healthy control participants (17–20) and participants with BPD (21–25), the results have been mixed. The dorsal anterior cingulate cortex (dACC) has been suggested as the source of rejection distress and social pain (17,26,27); however, more recently, brain regions other than the dACC (i.e., ventral ACC, orbitofrontal cortex, ventrolateral prefrontal cortex [PFC], posterior cingulate cortex, and the default mode network) have been argued to be important in social rejection (20,28,29). Furthermore, no study comparing healthy control participants and participants with BPD has demonstrated social rejection–specific differences in these (or any other) brain regions as would be expected if these regions were responsible for rejection distress (although nonspecific, rejection-independent differences between control participants and participants with BPD have been shown to exist in the Cyberball paradigm) (21–25,30).

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This heterogeneity of neuroimaging results stems in part from multiple conceptual and methodological problems in the original version of Cyberball. First, the vast majority of functional magnetic resonance imaging (fMRI) implementations of Cyberball have used block designs, where brain activity during exclusion blocks is subtracted from brain activity during inclusion blocks to isolate the brain regions that respond specifically to social exclusion. However, such designs make a strong, and typically incorrect, assumption that the control condition (i.e., social inclusion) differs from the experimental condition (i.e., social exclusion) by a single, specific mental process (i.e., the affective response to social rejection). If other cognitive processes that co-occur with exclusion-related affective responses (e.g., spatial attention, working memory, sensory processing, motor planning) also change between the experimental conditions, the cognitive subtraction between the experimental and control condition becomes difficult or even impossible to interpret (31). This problem is greatly reduced in event-related fMRI designs.

Second, the classic Cyberball game is characterized by a binary transition between 2 states, equal inclusion and complete exclusion. While binary transitions from inclusion to exclusion can occur in everyday life (e.g., when an individual offends their social group and is banned from all subsequent social interactions), the vast majority of social exclusion events vary in intensity and in degree of rejection distress. Accordingly, task designs with a binary transition between equal inclusion and complete exclusion have limited ecological validity. In addition, detection of a single binary transition from a low to a high exclusion rate has poor statistical power in fMRI, and the problem of poor statistical power is exacerbated by the low-frequency noise that is common in the long block designs used in most Cyberball paradigms (32,33). Thus, a more ecologically valid and statistically powerful fMRI implementation of Cyberball should include parametric modulation of exclusion probability from overinclusion to equal inclusion to varying degrees of exclusion.

Third, most prior implementations of Cyberball have used the experimentally controlled exclusion rate as an objective measure of social exclusion. However, both sensitivity and reactivity to social exclusion are fundamentally subjective and depend on an individual's perception and affective response to social exclusion. Moreover, because BPD is characterized by heightened sensitivity and elevated affective reactivity to social exclusion (9,11,12,25), the perceived exclusion probability could differ significantly between healthy control participants and participants with BPD. Therefore, a subjective measure of rejection distress would be a more appropriate and sensitive index of the exclusionary context than the objective exclusion probability.

Finally, prior Cyberball studies did not distinguish between neural responses to individual exclusion events and the overall exclusionary context related to the frequency of exclusion events over time (i.e., exclusionary context). The distinction between exclusion events and exclusionary context is essential for a meaningful interpretation of social exclusion–related brain activity because the exclusionary context could modulate the intensity of rejection distress and the associated brain response to any given exclusion event. For example, frequent inclusion could plausibly be protective, attenuating rejection distress that results from any particular exclusion event, while frequent exclusion could progressively exacerbate rejection distress to subsequent exclusion events. The converse could also be true; frequent inclusion could exacerbate rare rejection events, while frequent exclusion could desensitize, attenuating the distress associated with any single exclusion event. Furthermore, both the magnitude and direction of any modulation by exclusionary context might differ between healthy control participants and participants with BPD. For example, exclusionary context may modulate rejection distress and the associated brain response to individual exclusion events in control participants, but not participants with BPD or vice versa. Moreover, the degree to which heightened rejection distress in BPD is associated with maladaptive responses to exclusion events or impaired modulation of such responses by social context is currently unclear.

These conceptual and methodological issues have hindered the identification of the brain substrates of rejection distress in BPD that could act as plausible biomarkers and/or therapeutic targets. To address these problems, we designed a novel version of the Cyberball game optimized for fMRI, Cyberball+. Cyberball+ uses an event-related design with parametric modulation of exclusionary context ranging from overinclusion to equal inclusion to 3 levels of exclusion. In addition, instead of using the objective exclusion probability as the parametric modulator, we measured subjective rejection distress in response to each exclusionary context to account for the profound differences in rejection sensitivity between healthy control participants and participants with BPD.

This approach is a significant improvement over previous fMRI implementations of Cyberball because it includes a more ecologically valid range of exclusionary contexts, separates social exclusion–specific from nonspecific cognitive processes, dissociates exclusionary context from individual exclusion events, reduces sources of noise specific to block designs, and accounts for BPD-related differences in rejection sensitivity. We used this novel paradigm to test the following 2 hypotheses: 1) that healthy control participants and participants with BPD would show different patterns of neural responses to exclusion events and 2) that rejection distress would modulate the neural response to exclusion events differently in healthy control participants and participants with BPD.

METHODS AND MATERIALS

Participants

We recruited 23 women with DSM-IV diagnoses of BPD and 22 healthy control women ages 18 to 45 years via advertisements and referral through a large metropolitan hospital. The control group was groupwise matched on demographics and estimated IQ and was assessed with a semistructured interview to rule out a history of psychiatric disorders other than simple phobia. Exclusion criteria for the BPD group included a history of psychotic disorders, current major depressive episode, current substance use disorder, a suicide attempt within the last 6 months, or current use of psychotropic medications.

Procedure

Study procedures were approved by Columbia University's Institutional Review Board and conducted in accordance with

the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Clinical Assessment. To assess psychiatric history, BPD group participants completed the Structured Clinical Interview for DSM-IV, Patient Edition (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (34,35). Healthy control participants were assessed with the Structured Clinical Interview for DSM-IV Axis I–Non-Patient Edition. Healthy control participants were invited to participate if they had no substance use disorders and no present or past psychiatric disorders (with the exception of simple phobia). Recent assessor reliability studies within our research division yielded the following intraclass correlation coefficients (ICCs) for each DSM symptom criterion as a dimension (ICCs for the binary presence or absence of the diagnosis are shown in parentheses): Axis I diagnosis/SCID-I, ICC = 0.80 (0.70); Axis II diagnosis/SCID-II, ICC = 0.70 (0.70); BPD diagnosis, ICC = 0.89 (0.70). To estimate IQ, we used the vocabulary subtest of the Wechsler Adult Intelligence Scale (36). To assess trait rejection sensitivity, we used the Rejection Sensitivity Questionnaire (RSQ), which measures self-reported rejection anxiety and rejection expectation in hypothetical situations (37).

Cyberball+. We modified the original Cyberball game to be compatible with event-related fMRI design and parametric manipulation of exclusion probability. The participants were told that they would be playing a computerized ball-tossing game with 2 other players over a computer network (16,17,38). In reality, the participants played against a computer. To enhance credibility, the participants were shown an article describing a study that used a similar task (16,39) and were introduced to 2 confederates (co-authors JE and JG, White males aged between 30 and 45 years) who were described as the other 2 Cyberball+ players. They were chosen because they were in the age range of most participants and could be present for all fMRI scans.

We used the animated version of the game (16), in which 3 cartoon avatars are presented on the screen, the middle one representing the participant and the other two representing the virtual players (Figure S1). The participant could choose which virtual player to toss the ball to by pressing a button. Cyberball+ included five 3.5-minute runs. The exclusion rate for each run was varied by changing the frequency of ball throws to the participant such that the probability that players 1 and 2 threw the ball to each other rather than to the participant was 90% (high exclusion), 80% (moderate exclusion), 60% (low exclusion), 50% (equal inclusion), or 40% (over-inclusion). The experiment always started with 50% to establish a fair baseline, and subsequent runs were randomly counterbalanced.

Rejection Distress Questionnaire. To measure rejection distress after each Cyberball+ run, we used a 14-item questionnaire adapted from the Need-Threat Scale (5), which assesses the 4 fundamental social needs threatened by social exclusion: self-esteem, belonging, control, and meaningful existence (Figure 1). At the end of each run, participants were asked to rate, on a scale from 1 (not at all) to 5 (a great deal), how much they endorsed negatively valenced states that capture need threat (i.e., rejected, outsider, nonexistent, meaningless, angry, invisible, and disconnected) and positively valenced states that capture need satisfaction (i.e., included, good, liked, powerful, superior, in control, and self-esteem).

Data Analysis

Calculating Rejection Distress Scores. As a manipulation check, we tested the effects of exclusionary context (i.e., exclusion probability) and group on each item of the rejection distress questionnaire (Table S1). To derive a composite measure of rejection distress, we performed principal component analysis on the rejection distress questionnaire data. Cluster analysis of correlations among the 14 items revealed 3 main clusters, with one cluster encompassing need-threat items, a second cluster encompassing need-satisfaction items, and a third cluster consisting of a single item, "included" (Figure 2A). Principal component analysis of the rejection distress questionnaire data produced 3 principal components (PCs) with eigenvalues >1 that together accounted for 65% of the total variance (Figure 2B). Consistent with cluster analysis, PC1 accounted for the most variance (44%) and loaded positively on the need-threat items and negatively on the need-satisfaction items, suggesting that PC1 captured rejection distress (Figure 2C). In contrast, PC2 and PC3 loadings did not produce an obvious interpretable pattern. We calculated PC1 scores for each participant and for each exclusionary context (i.e., Cyberball+ run) as the dot product of individual item ratings and the PC1 eigenvector. We then used these context-specific rejection distress scores as the parametric modulator of the neural response in fMRI data analysis. Detailed analysis of the rejection distress questionnaire data is presented in the Supplement.

MRI Preprocessing and Analysis. Preprocessing is described in Supplemental Methods. First-level analysis included a whole-brain mass univariate general linear model with 3 event-related regressors: exclusion events, inclusion events, and button presses. Event durations for each regressor were convolved with participant-specific hemodynamic response functions (40), which were extracted from the participant's primary visual cortex using data from an independent visual emotion-processing task (41). Second-level analysis tested modulation of the neural response to exclusion events by rejection distress (i.e., context-specific PC1 scores). Third-level analysis tested group differences in the mean response to exclusion events and the modulation of that response by rejection distress.

RESULTS

Descriptive Data

The BPD and control groups did not differ in age, $t_{43} = 0.18$, $p = .859$ or estimated IQ, $t_{38} = 0.69$, $p = .492$, although the control group was slightly (mean of 1.2 years) more educated than the BPD group, $t_{43} = 2.25$, $p = .030$ (Table 1). In the BPD group, 30.5% of participants met criteria for past substance abuse or dependence, 47.8% met criteria for a past major depressive disorder, none met criteria for a current or past bipolar or posttraumatic stress disorder diagnosis, and 60%

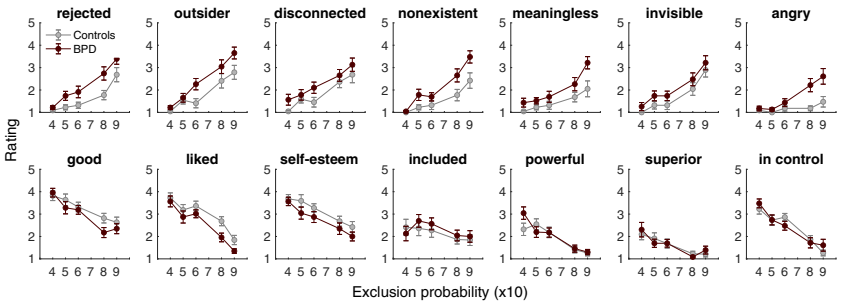

Figure 1. Rejection distress questionnaire ratings as a function of exclusion probability. Circles represent group means; error bars represent standard errors. BPD, borderline personality disorder.

had a history of psychiatric medication use. The mean number of BPD symptoms endorsed by the BPD group was 7.1 (SD = 1.2) (Figure S2A). The Global Assessment of Functioning Scale score was significantly lower ($p < 2 \times 10^{-12}$) for the BPD group (mean = 62.8, SD = 7.5) than for the control group (mean = 87.1, SD = 6.5) (Figure S2B). Participants with BPD scored higher than control participants on trait rejection sensitivity measured using the RSQ as follows: rejection anxiety, $t_{42} = 4.91$, $p < .001$; rejection expectation, $t_{42} = 5.53$, $p < .001$; and trait rejection sensitivity, $t_{42} = 5.62$, $p < .001$.

Modulation of Rejection Distress by Exclusionary Context

We tested the interaction between exclusionary context (i.e., exclusion probability) and group on rejection distress scores (i.e., PC1 scores) using a context × group analysis of variance. There was a main effect of exclusion probability ($F_{4,160} = 68.45$, $p < .001$, $\eta^2 = 0.63$) and a main effect of group ($F_{1,40} = 5.25$, $p = .027$, $\eta^2 = 0.12$) on rejection distress. Rejection distress increased as a function of exclusion probability (Figure 3A) and was higher in participants with BPD (Figure 3B). However, there was no context × group interaction on rejection distress, $F_{4,160} = 1.53$, $p > .1$, $\eta^2 = 0.04$. In addition, rejection distress correlated with RSQ scores as follows (Figure 3C): trait rejection sensitivity, $r = 0.36$, $p = .016$; trait rejection expectation, $r = 0.33$, $p = .027$; and trait rejection anxiety, $r = 0.28$, $p = .063$.

Neural Response to Exclusion Events

There was no group difference in the mean response to exclusion events across exclusionary contexts. The BPD group and the control group showed a similar pattern of activation to exclusion events relative to an implicit baseline across all 5 exclusionary contexts (Figure 4; Figure S3A). On average, exclusion events triggered activation in the rostromedial prefrontal cortex (rmPFC), the frontal poles, the premotor cortex, the precuneus, the posterior parietal cortex, and the lateral occipital cortex (Table S2).

Modulation of the Neural Response to Exclusion Events by Rejection Distress

In participants with BPD, but not in control participants, rejection distress inversely modulated the rmPFC response to exclusion events (Figure 4). A direct group comparison revealed a group difference in the modulation of the neural response to exclusion events by rejection distress in the rmPFC, the frontal pole, the precentral gyrus, and the postcentral gyrus (Figure 4; Figure S3B and Table S2). The location

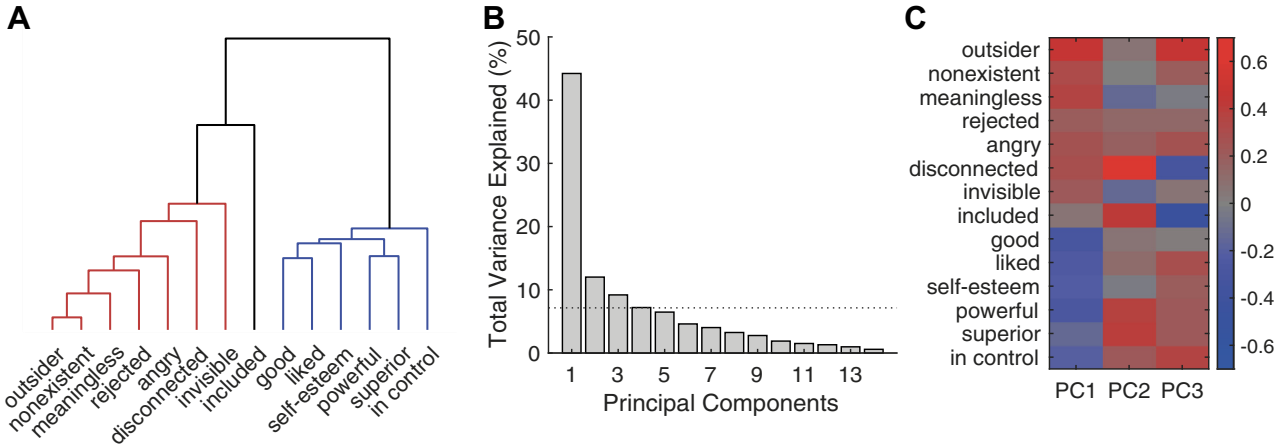

Figure 2. Cluster analysis and principal component (PC) analysis of the rejection distress questionnaire data. **(A)** Dendrogram showing the hierarchical clustering of the rejection distress questionnaire items. **(B)** Scree plot showing the percentage of total variance explained by each PC. The dotted line corresponds to an eigenvalue of 1. **(C)** Item loadings for the first 3 PCs.

Table 1. Participant Characteristics

Variable	BPD Group, n = 23	Control Group, n = 22
Age, Years, Mean (SD)	26.26 (4.94)	25.95 (6.45)
Race/Ethnicity, *n* (%)		
Asian	3 (13.04%)	5 (22.73%)
Black, non-Hispanic	4 (17.39%)	2 (9.09%)
Latinx/Hispanic	7 (30.44%)	7 (31.82%)
Multiple/other	1 (4.35%)	1 (4.55%)
White, non-Hispanic	8 (34.78%)	7 (31.82%)
Education, Years, Mean (SD)	14.83[a] (1.85)	16.05 (1.79)
Estimated IQ, Mean (SD)	52.16 (6.61)	50.48 (8.49)
RSQ Scores, Mean (SD)		
Rejection anxiety	4.26[b] (0.86)	2.76 (1.14)
Rejection expectation	3.18[b] (0.84)	2.01 (0.53)
Trait rejection sensitivity	13.83[b] (6.03)	5.76 (3.00)
GAF Score, Mean (SD)	62.78[b] (7.49)	84.77 (7.63)

BPD, borderline personality disorder; GAF, Global Assessment of Functioning; RSQ, Rejection Sensitivity Questionnaire.
[a]$p < .05$.
[b]$p < .001$.

of the rmPFC activation corresponds to a subset of the default mode network (Figure S4).

To visualize the direction of modulation, we conducted an exploratory region of interest (ROI) analysis. To generate an ROI, we used the intersection between voxels that were parametrically modulated by rejection distress in BPD and voxels that showed stronger modulation by rejection distress in participants with BPD versus control participants. We used the resulting ROI, which included the rmPFC (Figure 5A), to extract mean parameter estimates from the first-level statistic maps for the exclusion events versus baseline contrast. We then plotted the relationship between context-specific rejection distress and the extracted parameter estimates (Figure 5B). Due to nonindependence, we did not perform inferential statistics on the association between rejection distress and the parameter estimates extracted from the ROI (38).

Visual inspection of the scatter plot suggests that rejection distress was inversely associated with the rmPFC response to exclusion events in the BPD group. However, in the control group, the association was in the opposite direction. On average, parametric modulation of the rmPFC response by rejection distress was negative in the BPD group and positive in the control group (Figure 5C). In addition, the magnitude of the parametric modulation of the rmPFC response to exclusion events by rejection distress was associated with trait rejection expectation, $r = -0.30$, $p = .050$ (Figure 5D), but not trait rejection anxiety, $r = -0.17$, $p = .262$, or trait rejection sensitivity, $r = -0.26$, $p = .085$ measured using the RSQ.

DISCUSSION

By using Cyberball+ to parametrically modulate social exclusion, we were able to show that healthy control participants and participants with BPD displayed similar increases in rejection distress with increasing exclusion probability. However, rejection distress was consistently higher in the BPD group in every context except overinclusion. Although both groups showed a similar brain response to exclusion events, there was a group difference in the modulation of that response by rejection distress. As rejection distress increased, the rmPFC response to exclusion events decreased in the BPD group, but not in the control group. These results highlight the importance of distinguishing between the response to

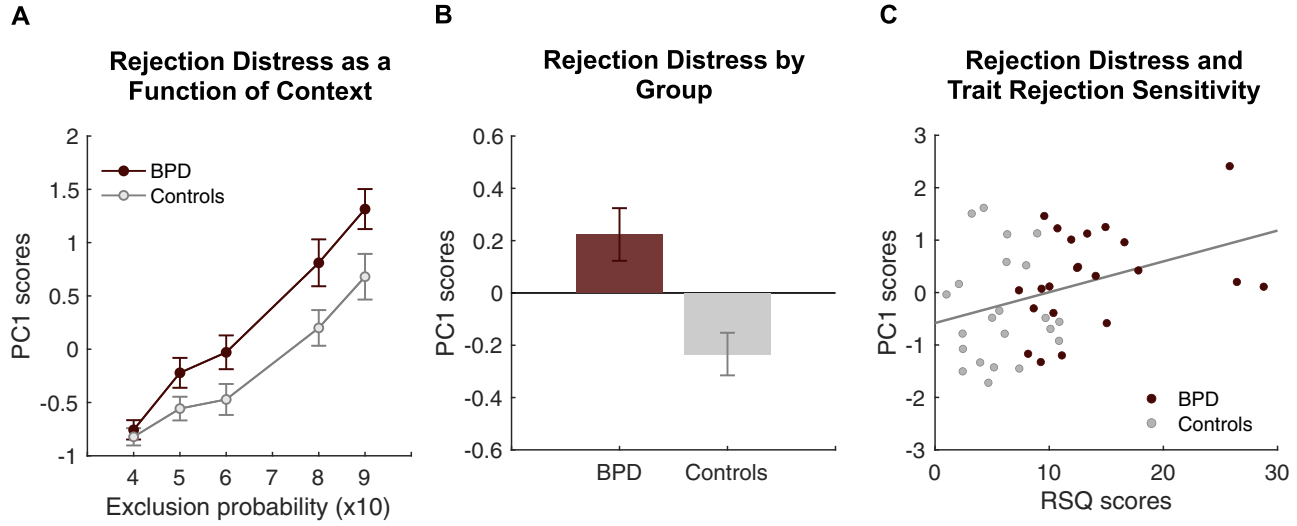

Figure 3. Context-specific rejection distress in participants with borderline personality disorder (BPD) and healthy control participants. **(A)** Rejection distress, indexed by context-specific principal component 1 (PC1) scores, increased as a function of exclusion probability. Circles represent group means; error bars represent standard errors. **(B)** Compared with control participants, the BPD group showed higher rejection distress across exclusionary contexts, indexed by PC1 scores. Bars represent group means; error bars represent standard errors. **(C)** Rejection distress across exclusionary contexts, indexed by PC1 scores, correlated with self-reported trait rejection sensitivity, indexed by Rejection Sensitivity Questionnaire (RSQ) scores.

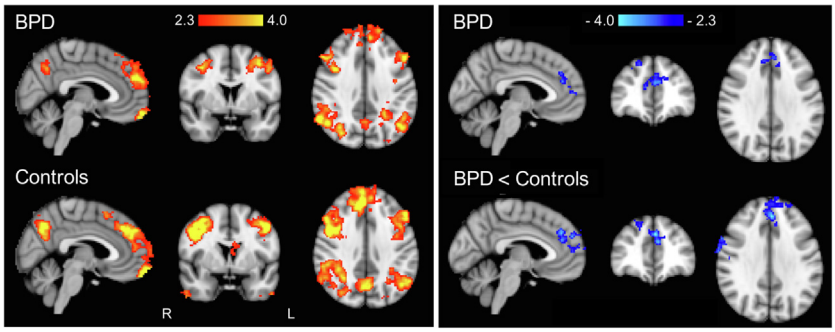

Figure 4. Neural responses to exclusion events. Left panel: Participants with borderline personality disorder (BPD) and healthy control participants showed a similar mean response to exclusion events averaged across the 5 exclusionary contexts (Montreal Neurological Institute standard space; color bar represents *Z* scores; cluster-forming threshold $Z = 2.3$; corrected cluster significance familywise error–corrected $p = .05$; minimum significant cluster size $k = 414$). Right panel: In participants with BPD but not in control participants, rejection distress parametrically modulated the neural response to exclusion events (Montreal Neurological Institute standard space; color bar represents *Z* scores; cluster-forming threshold $Z = 2.3$; corrected cluster significance familywise error–corrected $p = .05$; minimal significant cluster size $k = 326$). L, left; R, right.

individual exclusion events and the effects of the perceived social context.

Neuroimaging studies of social exclusion in nonclinical samples that used the classic block design of the Cyberball task, but no subjective or parametric measures of rejection distress, have reported associations between social exclusion and neural activity across a number of cortical structures, including the dACC (26), ventral ACC (42), orbitofrontal cortex (42), ventrolateral PFC (42), posterior cingulate cortex (41,42), posterior insula (41), and occipital pole (41). This variation in social exclusion–related activations in the literature may stem from the methodological limitations of the prior fMRI implementations of Cyberball, such as the use of block designs that are characterized by low signal-to-noise ratios and elevated false positive and false negative rates; the mixing of variance related to individual inclusion, exclusion, and motor events; an ecologically narrow range of exclusionary contexts; and the mixing of neural responses to exclusion events with the effects of exclusionary context. Our results suggest that the regions associated with rejection distress include the frontoparietal attention network and regions commonly involved in mentalization—two networks that are expected to be activated during social rejection. Interestingly, we found that the response in the dACC, an area previously argued to be involved in social pain, was not significantly increased during rejection events. This is consistent with previous work showing that the dACC is often activated nonspecifically across a variety of cognitive tasks (43–45) and recent meta-analyses of social exclusion studies (28).

More importantly, participants with BPD and control participants showed the same pattern of activity during rejection events. This is consistent with previous neuroimaging studies of BPD, all of which used the classic block Cyberball design and reported no significant differences between participants with BPD and control participants that were specific to social exclusion and/or rejection distress (21–25,30). However, it is important to note that these BPD studies had some of the same conceptual and statistical problems as those involving healthy control participants. Our results suggest that when these methodological problems are addressed, there are no differences in the neural response to exclusion events between healthy control participants and participants with BPD.

Despite a normative neural response to exclusion events, participants with BPD showed atypical modulation of this response by rejection distress. By dissociating exclusion events from exclusionary context, we were able to show that the rmPFC responded to rejection events and was modulated by the affective response to rejection. The rmPFC is part of the default mode network, which is involved in internally directed, self-referential, autobiographical, and theory-of-mind processes, especially those focused on the relationship between self and others, and episodic past and future events (46). The rmPFC is also a key node of a neural network implicated in mentalization, that is, the ability to reflect on the mental states of others and to infer mental states from behavior (Figure S5) (47–49). Given the role of the rmPFC in mentalization, decreasing rmPFC response to exclusion events with increasing rejection distress could reflect impaired mentalization, consistent with previously documented mentalization deficits in BPD. For example, a meta-analysis of mentalization studies has shown that people with BPD are significantly impaired in their ability to reason about mental states, particularly in complex social environments (50). Consistent with these findings, we have previously demonstrated (41,51) that participants with BPD show difficulties in probabilistic reasoning about the trustworthiness of others, which results in an appraisal bias favoring untrustworthiness. Moreover, these findings suggest that BPD is characterized by impaired interpretation of social context and ability to build accurate mental models of social interactions. These mentalization deficits may contribute to the maladaptive responses to social exclusion in BPD, such as heightened rejection distress.

An rmPFC-Mentalization-BPD Hypothesis

Social exclusion threatens fundamental social needs, such as belonging, self-esteem, control, and meaningful existence (5), and mentalization has been proposed as an adaptive coping response to social exclusion. Excluded individuals are motivated to regain a sense of connection to their social groups (42,52) and can employ mentalization to navigate complex social dynamics in an effort to reconnect (4,16,28,52,53–57). Accordingly, activity within the mentalization network has been associated with resilience to social exclusion and the nurturing and maintenance of strong social bonds (58). These results suggest that mentalization should be an important component during social exclusion and that the amount of mentalization required to cope with social exclusion should be related to the probability or intensity of the exclusion.

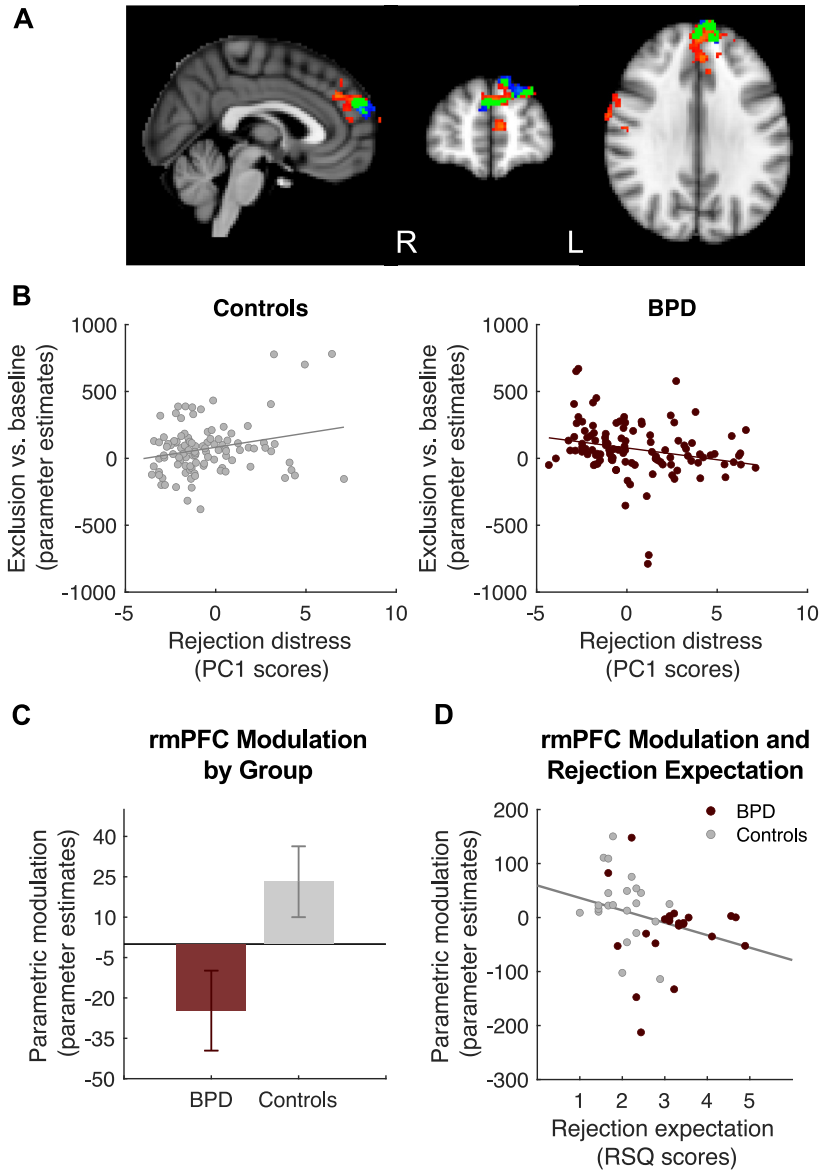

Figure 5. Modulation of the rostromedial prefrontal cortex (rmPFC) response to exclusion events by rejection distress. **(A)** Voxels within the rmPFC that were modulated by rejection distress in the borderline personality disorder (BPD) group (blue cluster) and that showed stronger modulation in participants with BPD vs. Control participants (red cluster) were used as a region of interest (ROI; green cluster). **(B)** As rejection distress increased, the rmPFC response to exclusion events increased in control participants but decreased in participants with BPD. Parameter estimates were extracted from first-level statistic maps for the exclusion vs. baseline contrast and averaged within the ROI. **(C)** The BPD group showed inverse modulation of the rmPFC response to exclusion events, whereas the control group showed the opposite pattern. Parameter estimates were extracted from second-level statistic maps for the parametric modulation contrast and averaged within the ROI. Bars represent means; error bars represent standard errors. **(D)** Modulation of the rmPFC response to exclusion events was inversely associated with self-reported rejection expectation measured using the Rejection Sensitivity Questionnaire (RSQ). Parameter estimates were extracted from second-level statistic maps for the parametric modulation contrast and averaged within the ROI. L, left; PC, principal component; R, right.

The inverse relationship in our sample between rejection distress and the neural response to exclusion events in a key node of the mentalization network is consistent with the model proposed by Luyten and Fonagy (59). It postulates that impaired mentalization is a core feature of BPD that results from dysfunctional coupling between rejection distress and mentalization and develops in the context of untrustworthy and unreliable social communication from early caregivers (58,60,61). Children exposed to such social environments may develop mentalization deficits that contribute to heightened rejection distress, which in turn further impairs mentalization, leading to yet more rejection distress, in a vicious cycle (58,62). When this cycle of inverse coupling between mentalization and rejection distress occurs repeatedly during development, a child may develop into an adult who is hypervigilant to social cues and tends to negatively interpret the motives of others. Our results are consistent with this model and suggest that a heightened tendency to expect rejection in BPD might stem from a failure to maintain or upregulate mentalization-related rmPFC activity during social exclusion.

An important limitation of our study is that there was no explicit measure of mentalization; thus, although the rmPFC is a well-known node of the mentalization network, we cannot conclude with certainty that the rmPFC activity differences between control participants and participants with BPD are specifically related to differences in mentalization. Second, while we measured trait rejection sensitivity and contextual state changes in rejection distress, it is possible that other

rejection-related events experienced by participants immediately prior to testing could also modulate the contextual changes in rejection distress, thereby adding additional noise to our rejection distress estimates. Third, although participants with BPD were carefully screened for current depressive episodes, were not taking psychotropic medications, and were rigorously matched to healthy control participants, our study did not include a psychiatric control group, and consequently the specificity of our findings to BPD remains to be confirmed. Fourth, the sample sizes of both groups were relatively small and may raise concern about statistical power; nevertheless, this concern is somewhat mitigated by the methodological improvements from our event-related design, the large number of trials per participant (>700 trials), and the participant-derived hemodynamic response functions used to model the neural activity, which reduce both noise and bias (40,63). Fifth, because our BPD group consisted entirely of women, the generalizability of our results to men with BPD is unknown. Finally, it is important to emphasize that a neural abnormality in the mentalization network does not imply that mentalization-based psychotherapies are optimal or even appropriate for treating this specific deficit, and the relationship between rmPFC abnormalities and how such abnormalities respond to different types of treatment will require future investigations.

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ARTICLE INFORMATION

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