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Elevated Neurobehavioral Responses to Negative Social Interactions in Women with Bulimia Nervosa

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Abstract

Background: Bulimia nervosa (BN) is a complex psychiatric illness that includes binge-purge behaviors and a belief that one's value as a person depends on body shape and weight. Social pressure strongly influences the development and maintenance of BN, but how this manifests neurobiologically within an individual remains unknown. We utilized a computational psychiatry approach to evaluate neural mechanisms underlying social interactions in BN.

Methods: Behavioral and functional magnetic resonance imaging data were collected from 24 women with BN and 26 healthy comparison women (HC) using an iterated social-exchange game. Data were sorted round-by-round based on whether the mathematically-computed social signals indicated an improving (positive reciprocity) or deteriorating relationship (negative reciprocity) for each participant.

Results: Social interactions with negative reciprocity resulted in more negative behavioral responses and stronger neural activations in both cortical and subcortical regions in BN than HC. No behavioral or neural differences were observed for interactions demonstrating positive reciprocity, suggesting a very specific form of psychopathology in BN: amplification of negative self-relevant social interactions. Cortical activations (e.g., temporoparietal junction and

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Disclosures

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dorsolateral prefrontal cortex) did not covary with mood symptoms while subcortical activations (e.g., amygdala and dorsal striatum) were associated with acute psychopathology.

Conclusions: These data provide a first step toward a mechanistic neuropsychological model of aberrant social processing in BN, demonstrating how a computational psychiatric approach can elucidate neural mechanisms for complex psychiatric illnesses. Future treatments for BN may include targeting neural regions that support these negative biases in social perceptions.

Keywords

Bulimia nervosa; eating disorder; reciprocity; social interaction; negativity bias; neuroimaging

Introduction

Bulimia nervosa (BN) is a serious mental illness in which excessive dependence of self-worth on body size is proposed to drive a restrict-binge-purge eating disorder cycle (1, 2). Social pressures related to body-image have been associated with the development of eating disorder behaviors. Specifically, importing the Western thin-ideal via television rapidly led to bulimic behaviors within adolescents in a culture, Fiji, in which they previously did not exist (3). Critically, follow-up studies then demonstrated that these eating disorder behaviors in adolescents in Fiji were related to both one's perceived peer norms about body-image and sensitivity to peer influence (4). In prevention research, the only evidence-based intervention that reduces the development of eating disorders combats inappropriate social norms about body image using cognitive dissonance exercises delivered in small groups of one's peers (5). In concert, these studies suggest that altered processing during social interactions, sensitivity to peer pressure, may be fundamental to the pathology of BN.

Although structural and functional abnormalities have been observed in frontostriatal circuits during both cognitive and reward-based tasks in BN (reviewed in 6), little work has evaluated the neurobiological mechanisms underlying social processing in BN. One study considered social vs. non-social processing by asking participants to evaluate geometric shapes identified either as people or inanimate objects, reporting diminished responses in the BN cohort relative to controls for the people condition in the temporoparietal junction (TPJ) (7), a region associated with reasoning about the mental states of others (i.e., theory of mind) (8) and attention (9). Another study showed greater activation in anterior cingulate cortex (ACC) in BN than in controls when viewing unpleasant social descriptors (10). However, neither of these social tasks asked the participants to think about themselves in relation to the social stimuli or simulated real-world social interactions, limiting their ability to evaluate social behaviors.

By combining economic game theory with functional magnetic resonance imaging (fMRI), the neuropsychological processes involved in social behaviors can be quantitatively assessed (11–13). The multi-round trust (MRT) game mimics the process of building a relationship with another person — two players repeatedly interact within the constraints of an economic investment game. One player decides how much money to invest to the other; the other as the trustee decides how much to repay. Since there are multiple rounds in the game, expectations about the other person develop over the course of these interactions, akin

to those in any other human relationship. The quality of each interaction in the MRT depends heavily on reciprocity — a quantity that assesses whether the increase/decrease in repayment from the trustee in a previous round was reciprocated by a more generous/selfish investment (12, 14). A more generous investment yields positive reciprocity and suggests an improvement in the relationship, while a more selfish investment exhibits negative reciprocity and suggests a deterioration of the relationship (12, 14). Neural data from the MRT has suggested that the dorsal striatum (DS), amygdala, anterior insula and intraparietal sulcus are involved in perceiving and responding to reciprocity (11, 14–17), and other task-induced activations in ventromedial prefrontal cortex, dorsomedial prefrontal cortex, TPJ, ACC, and dorsolateral prefrontal cortex (dlPFC) appear related to mentalizing and cognitive control (14, 18–20).

Here, we investigated behavioral and neural responses of women with BN engaged in the MRT during fMRI scanning. Previously, in anorexia nervosa (AN), another eating disorder, both women with and recovered from AN had reduced responses in precuneus and right angular gyrus to positive reciprocity in the MRT, suggesting that deficits in the perception of kindness could be a trait related to AN (12). However, differences in interpersonal function have been observed across these two eating disorders, with AN associated more with social anxiety and BN characterized by more negative interpersonal relationships (21). Thus, we hypothesized that participants with BN would be more sensitive, neurally and behaviorally, to negative reciprocity in the MRT than healthy comparison women (HC). By assessing the responses to positive and negative reciprocity, the indicators of improvement and deterioration of the social relationship respectively, we evaluate neural components of the aberrant processing of social interactions in BN.

Methods and Materials

Participants

Twenty-four women with BN and 26 HC women participated, with age (recruitment range, 18–46 years) and body mass index (BMI) matched (Table 1). HC participants were recruited using flyers and advertisements at UT Southwestern. Participants with BN were recruited through support groups or clinicians in the community, and were not required to be in any particular form of treatment. All participants provided written informed consent at first visit. The study was approved by the institutional review board at UT Southwestern Medical Center. Eating disorder diagnoses were determined using *DSM-5 Eating Disorder Assessment* (22, 23) and other DSM-5 diagnoses were established using the *Mini-International Neuropsychiatric Interview for DSM-5* (MINI) (24).

Inclusion/Exclusion Criteria.—Inclusion as a HC subject required no current DSM-5 psychiatric diagnoses and no lifetime eating disorder diagnoses or first-degree relatives with eating disorders. Inclusion as a BN participant required current BN diagnosis, no lifetime psychotic illnesses or bipolar I disorder, no substance use disorders in the prior six months, and not meeting DSM-5 criteria for AN during prior year. Eight participants in the BN group had had AN in their lifetime. The *Wechsler Abbreviated Scale of Intelligence* (WASI) (25) assessed intelligence, with minimum of 75 was required for participation. Participants on

antidepressant medications were permitted, if medication dose was stable for at least one month prior to scan.

Self-Reported Assessments

Clinical diagnoses and inclusion/exclusion criteria were assessed at first visit, and an MRI scan was scheduled for second visit. Seventy-two hours before the scan, participants received a REDCap (26) link with a set of self-report scales including Eating Disorder Examination Questionnaire (EDE-Q) (27), Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) (28), and Internal, Personal, and Situational Attribution Questionnaire (IPSAQ) (29). Following the scan, clinician-administered quantitative assessments for current depression (Quick Inventory of Depression, Clinician-Report [QIDS-CR] (30)), and anxiety (Structured Inventory of Generalized Hamilton Anxiety Symptoms [SIGH-A] (31)) were obtained.

Experimental Procedure

Each participant played the trustee role in the MRT with an anonymous investor (computer-simulated, but presented to participants as a real person) in the scanner for 10 rounds (one functional run; approximately 10 minutes). In each round, the investor offered a portion of 20 monetary units (drawn from known responses from real players as described in (11) with a k-nearest neighbors sampling algorithm) to the participant. This amount of money was tripled and sent to the participant who decided how much to repay. At the end of each round, participants were asked to rate how they felt about that round using emoticons ranging from unhappy to happy on a 1–9 scale (Figure 1A).

Behavioral data analysis

BN and HC groups were compared in social interactions received (i.e., average investment, positive reciprocity, negative reciprocity) and overall behavioral responses (i.e., average repayment, emotion rating, total earning).

The reciprocity of the investment in each trial was defined as the difference of the current change in investment (ΔI_t) in response to the previous change in repayment (ΔR_{t-1}) (12, 14) (details in Supplementary Methods). An investment with positive reciprocity ($\Delta I_t > \Delta R_{t-1}$) indicates an improving relationship, while an investment with negative reciprocity ($\Delta I_t < \Delta R_{t-1}$) suggests a worsening relationship (Figure 1B), relative to the participant.

Linear mixed-model regressions evaluated group differences in the effects of positive and negative reciprocity on the change in repayment or emotion rating. First, a set of mixed-model regressions were implemented, with group (BN/HC), positive reciprocity ($\Delta I_t - \Delta R_{t-1}$ when $\Delta I_t > \Delta R_{t-1}$; 0 when $\Delta I_t \leq \Delta R_{t-1}$), and negative reciprocity ($\Delta I_t - \Delta R_{t-1}$ *when* $\Delta I_t < \Delta R_{t-1}$; 0 when $\Delta I_t \geq \Delta R_{t-1}$) as predictors, and change in repayment (ΔR_t) as the dependent variable. Second, another set of mixed-model regressions were implemented to compare group difference in the effects of positive and negative reciprocity on the change in emotion (details in Supplementary Methods).

Neuroimaging data acquisition and preprocessing

Images were acquired with a 3T Philips Achieva MRI scanner, using a 1-shot gradient T2*-weighted echo-planar image sequence with a repetition time (TR) of 2 s. The echo time (TE) was 25 ms, and the flip angle was 90°. Volumes were composed of 38 axial slices. Each slice was acquired with a matrix size of 64 × 64 and a voxel size of 3.4 × 3.4 × 4 mm. High-resolution MP-RAGE 3D T1-weighted images were acquired with the following imaging parameters: TR = 8100 ms, TE = 3.7 ms; a 12° flip angle, and 1 mm^3 voxels. Image preprocessing was implemented in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) following standard procedures (details in Supplementary Methods).

Reciprocity-induced whole-brain activation

General linear models (GLM) were specified for each participant. To investigate the neural responses to positive and negative reciprocity respectively, the investments were sorted by the valence of reciprocity into three types of events: positive reciprocity, negative reciprocity, and other investments (the first two investments for which reciprocity could not be calculated for the lack of earlier interactions, and those with reciprocity = 0). These events, all other visual stimuli, and motor responses were modeled in the design matrix by convolving each event onset with a canonical hemodynamic response function in SPM12. Residual effects of head motion were corrected by including the estimated six motion parameters for each participant as covariates.

Beta maps were estimated for each regressor for each participant and then entered into second-level random effect analyses. First, the whole-brain responses to investments with positive and negative reciprocity were compared between BN and HC. Contrasts include $BN_{neg} – HC_{neg}$, $BN_{pos} – HC_{pos}$, and $(BN_{neg} – BN_{pos}) – (HC_{neg} – HC_{pos})$. Second, given that comorbid conditions related to depression and anxiety are common among patients with eating disorders (32), we explored associations between acute clinical symptoms and neural responses by including each assessment (EDE-Q, QIDS-CR, and SIGH-A) as a covariate in a group-level model for negative reciprocity, pooling all participants.

Statistics maps were overlaid on a standard brain in MNI space using Mango (http://ric.uthscsa.edu/mango/mango.html), and projected to the mid-thickness surface of the Human Connectome Project 900 subject group average using Connectome Workbench version 1.2.3 (https://www.humanconnectome.org/software/get-connectome-workbench).

Clinical symptom region of interest (ROI) analyses

First, we explored whether negative-reciprocity-induced activations were related to BN-specific symptoms during the 28 days prior to the scan, including number of episodes of binge-eating, vomiting, laxative use, and excessive exercise. Based on brain regions associated with reciprocity in the MRT identified by a previous meta-analysis (17), we created four spherical masks centered at the reported peaks with 6 mm radius: fusiform gyrus (center: [48, −60 −12]), right anterior insula (center: [34 18 −8]), intraparietal sulcus (center: [32 −60 44]), and inferior occipital gyrus (center: [30 −94 −8]). For each ROI, a step-wise linear regression was conducted to evaluate which symptoms (independent

variables) were predictive of the average of beta values for negative reciprocity in all voxels within the mask (dependent variable), pooling all participants.

Second, because the activations in subcortical areas (i.e., amygdala and DS) following negative reciprocity were stronger in BN than HC, and covary with depression (Figure 2&3), the association between subcortical responses and self-reported emotion were explored. A mask for bilateral amygdala was defined by AAL3 (33); a mask for DS was obtained from Oxford-GSK-Imanova structural striatal atlas (34). We tested correlations between investment-induced activations within these two ROIs and the change in emotion rating by pooling all rounds for BN and HC respectively (details in Supplementary Methods).

Statistical Analysis

Statistical comparisons between BN and HC were implemented using SPSS (IBM SPSS Statistics Version 21.0, IBM Corp.), with independent-samples *t* tests, for demographic information, clinical assessments and overall behavioral measures. Step-wise linear regressions and correlations (*Pearson* correlation, multiple comparisons corrected by *Benjamini–Hochberg* false discovery rate [FDR]) in ROI analyses were also conducted with SPSS. Mixed-model regressions were implemented with *lme4* (35) and *lmerTest* (36) in Rstudio (37) (version 1.0.136). Significance was set at $p < .05$, two-tailed. Threshold for whole-brain analyses was set at $p < 0.05$, family-wise error (FWE) cluster-wise corrected (cluster-defining threshold, $p < 0.001$), unless otherwise stated.

Results

Participants

BN and HC were not significantly different in intelligence, age, or BMI. In the BN cohort, fifteen had recurrent major depressive disorder with six meeting criteria for an episode of major depression at the time of the scan; twelve had a comorbid anxiety disorder (generalized anxiety disorder, agoraphobia, panic disorder, social anxiety disorder); three had obsessive-compulsive disorder, and four had post-traumatic stress disorder. No one in the HC cohort had any psychiatric disorders. Antidepressant medications were utilized by 15 participants in the BN cohort and one in the HC cohort.

Self-Reported Assessments

The BN and HC groups differed on all clinical measures: eating disorder symptoms (EDE-Q), depression (QIDS-CR), and anxiety (SIGHA). BN scored higher for both reward sensitivity, punishment sensitivity, and had a more negative self-attribution bias (IPSAQ, externalizing bias) than HC (Table 1).

Behavioral Results

There were no group differences in social interactions received (i.e., average investment, positive reciprocity, negative reciprocity) or overall behavioral responses (average repayment, emotion rating, or total earning), nor in the impact of negative or positive reciprocity on the change in emotion (details in Supplementary Results).

However, as shown in Figure 1C, BN's change in repayment was more sensitive to negative reciprocity than HC (BN, coefficient (β) = 0.34; HC, β = 0.10; BN vs. HC, β = 0.24; $t(347)$=1.99; p = 0.047; *95% CI*, 0.00 – 0.48), while no group difference was found for positive reciprocity (BN, β = 0.22; HC, β = 0.15; BN vs. HC, β = 0.07; $t(347)$= 0.58; p = 0.562; *95% CI*, −0.04 – 0.13). Specifically, when experiencing a higher negative reciprocity, BN reduced repayment more than HC.

Whole-Brain Analysis

First, compared to HC, the BN group had stronger activations for negative reciprocity in left TPJ, left dlPFC, middle cingulate cortex (MCC), precuneus, insula, bilateral amygdala, DS, pons, lingual gyrus and cerebellum, while no group difference was found for positive reciprocity (Figure 2; Table S1). Supporting this result, the HC group had a deactivation or no activations for negative reciprocity in these regions while the BN group showed significant activations in these regions (Figure S1), whereas a similar whole-brain activation pattern is observed for both cohorts in response to positive reciprocity (Figure S2). After controlling for age, group difference remained in all clusters except for the right amygdala (Figure S3 & Table S2). No brain areas showed a greater activation in HC than BN for positive or negative reciprocity. Cross-cohort brain activations based on valence of reciprocity (contrast: $[BN_{neg} – BN_{pos}] – [HC_{neg} – HC_{pos}]$) also supported stronger activations in left TPJ and MCC in BN than HC for negative reciprocity against positive reciprocity (Figure S4 & Supplementary Results), while no neural regions showed stronger activations for HC than BN in this contrast.

Second, whole-brain regressions explored whether acute clinical symptoms, including eating disorder, depression, and anxiety, were related to neural activations to negative reciprocity across all participants. Activations in the right amygdala and bilateral DS (peak intensity = 4.95; peak at [28, 16, −10]; number of voxels (k) = 2111) were positively correlated with overall severity of eating disorder ($p_{FWE} < 0.05$, cluster-defining $p < 0.005$; Figure 3A). Activations in the bilateral amygdala and DS (cluster 1: peak intensity = 4.52, peak at [−26, −4, −12], k = 1106; cluster 2: peak intensity = 4.11, peak at [22, 12, 6], k = 1086) were positively correlated with depression ($p_{FWE} < 0.05$, cluster-defining $p < 0.005$; Figure 3B). No significant clusters were observed in whole-brain regression of anxiety symptoms in relation to negative reciprocity. Figure 3C&D show the overlap of regions identified from the whole-brain group differences (Figure 2) with clinical symptom measures; many regions remain different based on group (red).

Clinical Symptom ROI Analyses

The step-wise regressions found that the number of binge-eating episodes during the 28 days prior to the scan was associated with a stronger activation in the intraparietal sulcus for negative reciprocity across all participants (β = 0.26, t = 2.45, p = 0.019; Figure S5).

Separately, the activation in amygdala for each investment was negatively correlated with the change in emotion in BN (r = −0.23, p_{FDR} = 0.004), but not in HC (r = −0.01, p_{FDR} > 0.05). The DS activation was also negatively correlated with the change in emotion in BN (r

= −0.15, p_{FDR} = 0.048), but not in HC (r = 0.002, p_{FDR} > 0.05) (Figure S6), suggesting that the stronger subcortical responses were related to a more negative emotional state in BN.

Discussion

Although overvaluation of the thin-ideal is a sociocultural construct related to BN and difficulties in social relationships are common in BN (38), neural mechanisms that alter social processing in BN have been unknown. Using fMRI with an iterated social exchange game, the current study found that women with BN were more reactive to negative reciprocity than HC, but showed no differences following positive reciprocity. The BN group had increased neural activations in both cortical (TPJ, dlPFC, MCC, precuneus, insula, and lingual gyrus) and subcortical (bilateral amygdala, DS and pons) regions after experiencing negative reciprocity. Activations for negative reciprocity in the cortical areas did not covary with mood symptoms, while those in the subcortical areas were positively correlated with depression, as well as overall severity of eating disorder symptoms, leading to a two-level neuropsychological model for the aberrant processing of social interaction in BN (Figure 4).

Clinical studies have reported a negative bias in BN, and even connected binge-eating episodes specifically to negative social interactions (39). Computationally, BN here showed a steeper slope between negative reciprocity and the change in repayment, demonstrating more negative reactivity, i.e., withholding money. In contrast, the two groups did not differ in the average repayment or emotion rating, indicating that the sensitivity in BN is highly specific for negative social interactions, not a persistent negativity toward all social interactions or a fixed negative mood irrespective of social circumstances. This heightened sensitivity about negative feedback may contribute to development of a negative body-image and support cognitive preoccupations about meeting sociocultural expectations.

Stronger activations in the cortical areas (e.g., TPJ and dlPFC) for negative reciprocity did not covary with mood symptoms, suggesting functional alterations of these regions may be part of core features of BN. Of particular interest is the TPJ which was more active following positive than negative reciprocity in the HC cohort while the reverse was seen in BN (Figure S1, S2 & S4). The TPJ is widely considered as part of the attention network implicated in attentional orienting toward salient events (9). Our finding suggests enhanced attention to negative reciprocity in BN, which echoes a prior study showing greater attention bias toward negative social stimuli (e.g., angry faces) in BN (40), whereas HC appear to reduce attentional allocation to negative social stimuli. The TPJ is also associated with theory of mind (8, 41), which might be engaged to determine the appropriate social response, with BN mentalizing more about negative interactions. Previous studies of BN (see (42) for a meta-analysis) have reported only modest deficits in theory of mind, but most studies have used paradigms that do not allow social interactions, such as reading emotion from viewing the eyes of a stranger (43, 44) or hypothesizing social reasoning related to abstract scenarios (45). The MRT involves simulation of a relationship that the participant is involved in, adding self-relevance into the social cognitive process, a technique that can capture clinically-relevant social impairments.

Functional and structural abnormalities in fronto-striatal control systems, of which the dlPFC is a crucial node, have been found consistently in BN (46, 47). Binge-purge episodes have been connected to local volume reductions in frontal regions (insula, inferior and medial frontal gyri) and inferior parietal cortex (48, 49). Repetitive transcranial magnetic stimulation (rTMS) in the dlPFC was found effective in reducing cue-induced food craving and binge eating in people with BN (50), suggesting dysfunctional cognitive control systems may contribute to binge eating and other impulsive behaviors in BN (51). Our finding extends this conjecture into the social domain, as dlPFC may also play an important role in encoding responses to negative social signals.

The increased subcortical activations following negative reciprocity, and their positive correlations with depression, suggests altered emotional processing of negative social stimuli also occurs in BN. Elevated activations in amygdala and DS to negative emotional stimuli have constantly been found in individuals with depression (52), and associated with attentional bias toward and exaggeration of negative events (53). A study on people with depression found that the sadness of facial expressions was accompanied by increasing activation in amygdala and putamen (54). Here, stronger responses in amygdala and DS were associated with increased self-reported negative feelings in BN but not in HC, suggesting increased negative emotions after negative reciprocity.

An earlier study in AN found reduced responses to positive reciprocity in angular gyrus and precuneus, using the MRT (12). AN and BN are both eating disorders, but the eating behavior that dominates the illnesses differ; AN is dominated by restrictive eating, whereas BN is defined by frequent binge-purge behaviors. Mechanistically, a heightened sensitivity to negative events, as observed in BN here, may differ from a diminished response to positive events, as previously observed in AN, but the impact of both problems may converge in real life, such that establishing and maintaining social support is a challenge in both eating disorders (55, 56).

There are many limitations to the study. Even though our findings survive appropriate statistical thresholds, the sample size of our study is relatively modest. Therefore, the results should be interpreted and generalized cautiously. All participants here are females, so mechanisms in men with BN remain unknown. In addition, many BN participants were taking antidepressants; we compared participants on antidepressants to those not on antidepressants in both whole-brain and ROI analyses, and found no significant differences (Supplementary Results). Also making it unlikely that findings are related to medications, a meta-analysis found that antidepressants increased activity to positive stimuli and decreased activity to negative stimuli in mood-disorder patients' emotional network (57), the opposite direction as observed here for BN.

In sum, we find that women with BN have stronger neural and behavioral reactions to negative social signals, and no differences in processing positive social signals. This enhanced reaction toward negativity, was observed in cortical areas involved in attention, theory of mind, and cognitive control and subcortical regions related to emotion processing in BN. Functional alterations in cortical areas in which the enhanced activations for negative reciprocity did not covary with mood symptoms, might be part of core features involved in

BN. This neural bias toward negative socio-emotional processing is likely to contribute to dissatisfaction with social relationships, and impaired quality of life in BN. Treatments for BN may benefit from increasing awareness and insight into this negative social processing bias. Recently, a brief group therapy targeting social biases also led to positive changes in acute psychopathology in a pilot cohort of eating disorder patients, supporting explicit inclusion of these concepts in the treatment of eating disorders (58). Finally, these results support consideration of these cortical neural regions, the TPJ, MCC, and dlPFC, as potential targets for neuromodulatory interventions in BN, as well as provide possible biomarkers of treatment responses. Previous studies have observed the effect of rTMS in the dlPFC in reducing cue-induced food craving and binge eating in people with BN (50, 59). Future studies may explore if and how activating or deactivating TPJ and MCC by brain stimulation treatments can affect BN's social behaviors and improve clinical symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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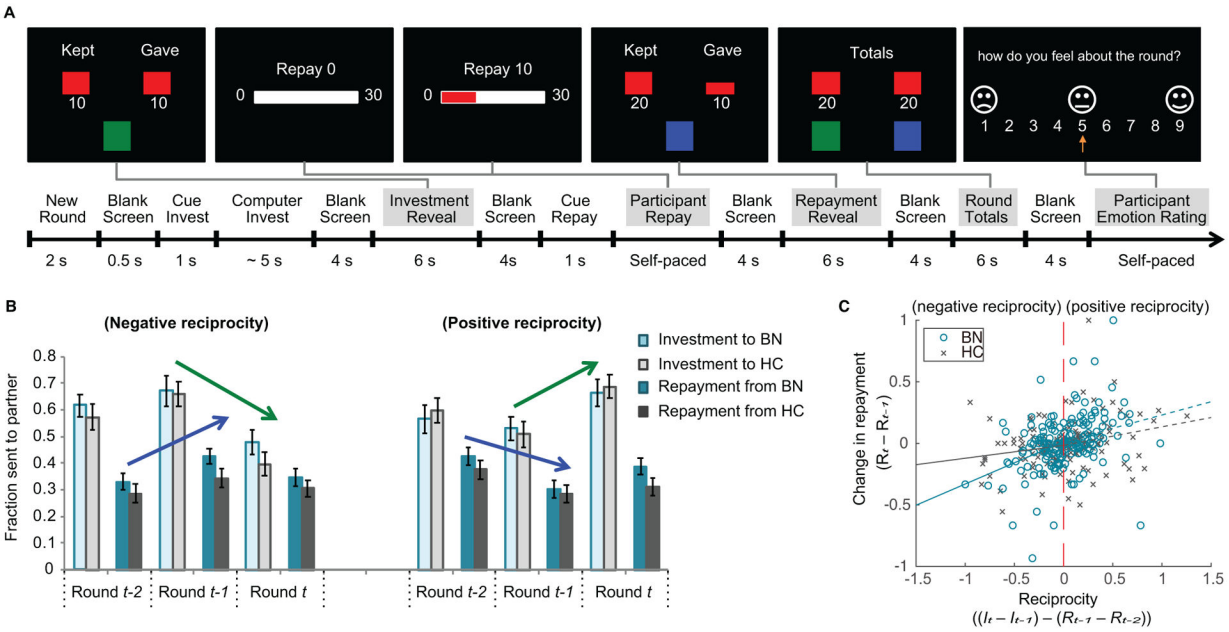

Figure 1.

The multi-round trust game (MRT) and behavioral results. **A.** Schematic illustrating one round of the MRT. **B**. The fraction of investment and repayment (scaled by the amount available to send) averaged for each group of participants sorted by the sign of reciprocity in the investment. The reciprocity of an investment was defined as the difference between the current change in the investment ($\Delta I_t = I_t - I_{t-1}$) and the previous change in the repayment ($\Delta R_{t-1} = R_{t-1} - R_{t-2}$). For both groups, in rounds with negative reciprocity ($\Delta I_t < \Delta R_{t-1}$), the repayment fraction increased (upward blue arrow) but the investment fraction decreased (downward green arrow), while in rounds with positive reciprocity ($\Delta I_t > \Delta R_{t-1}$), the repayment fraction decreased (downward blue arrow) but the investment increased (upward green arrow). **C**. Change in repayment as a function of reciprocity in each round of the game. Negative reciprocity was more predictive of the change in repayment in BN than in HC, while no difference was found in rounds with positive reciprocity. Trend lines for negative reciprocity (solid lines) and positive reciprocity (dotted lines) in BN (dark green) and HC (gray) were plotted according to the intercepts and slopes derived from the fixed effect of mixed-model regressions: negative reciprocity in BN, y = 0.34x + 0.01; negative reciprocity in HC, y = 0.1x − 0.02; positive reciprocity in BN, y = 0.22x + 0.01; positive reciprocity in HC, y = 0.15x − 0.02. BN, bulimia nervosa; HC, healthy comparison women.

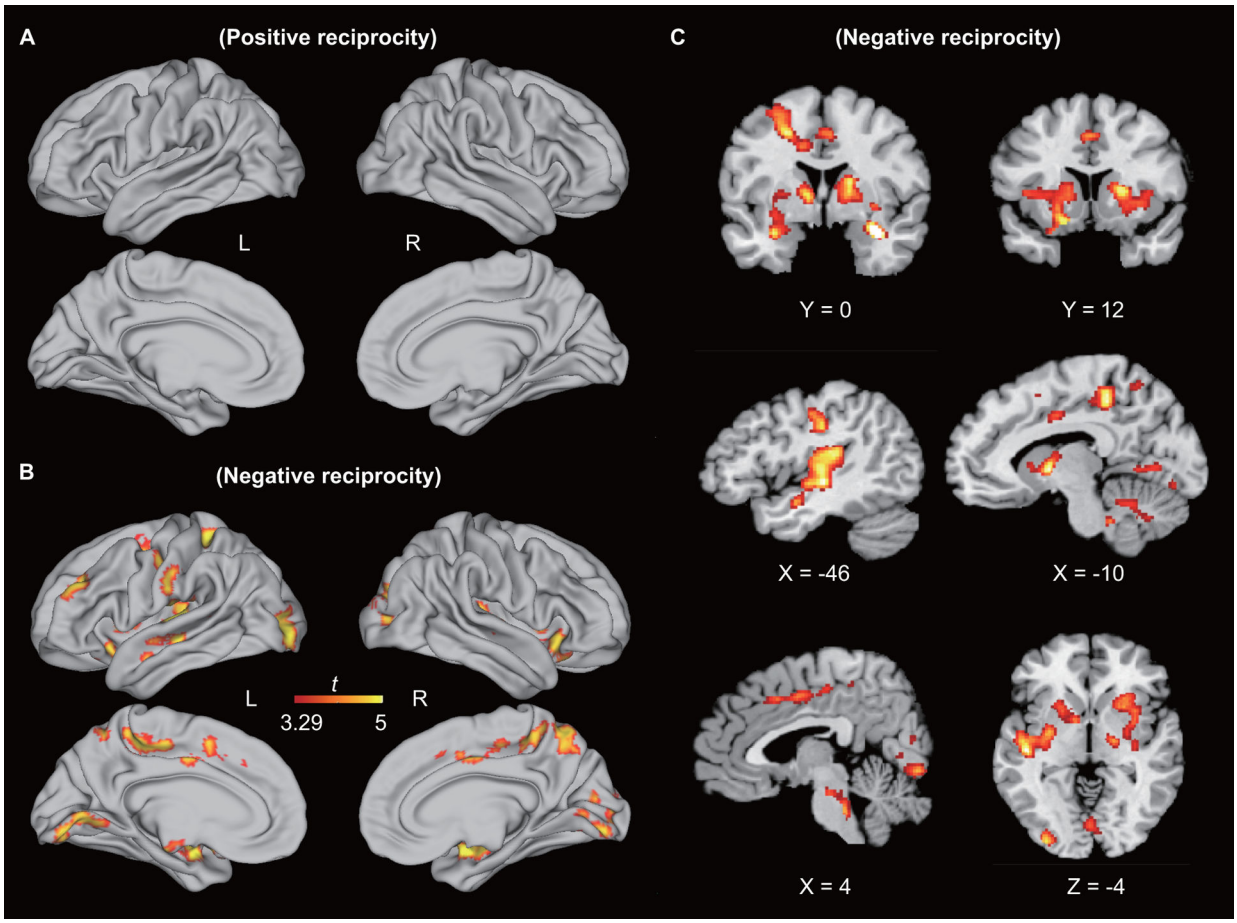

Figure 2.

Group differences in the neural responses to positive reciprocity and negative reciprocity. **A**. No significant cluster for positive reciprocity (surface view). **B & C** Surface view (B) and slice view (C) for negative reciprocity. The bulimia nervosa (BN) group, compared to healthy comparison women (HC), had stronger activations in left temporoparietal junction (TPJ), left dorsolateral prefrontal cortex (dlPFC), middle cingulate cortex (MCC), precuneus, insula, lingual gyrus and cerebellum for negative reciprocity (details in Table S1). All images shown at FWE cluster-wise corrected $p < 0.05$ with a cluster-defining $p < 0.001$.

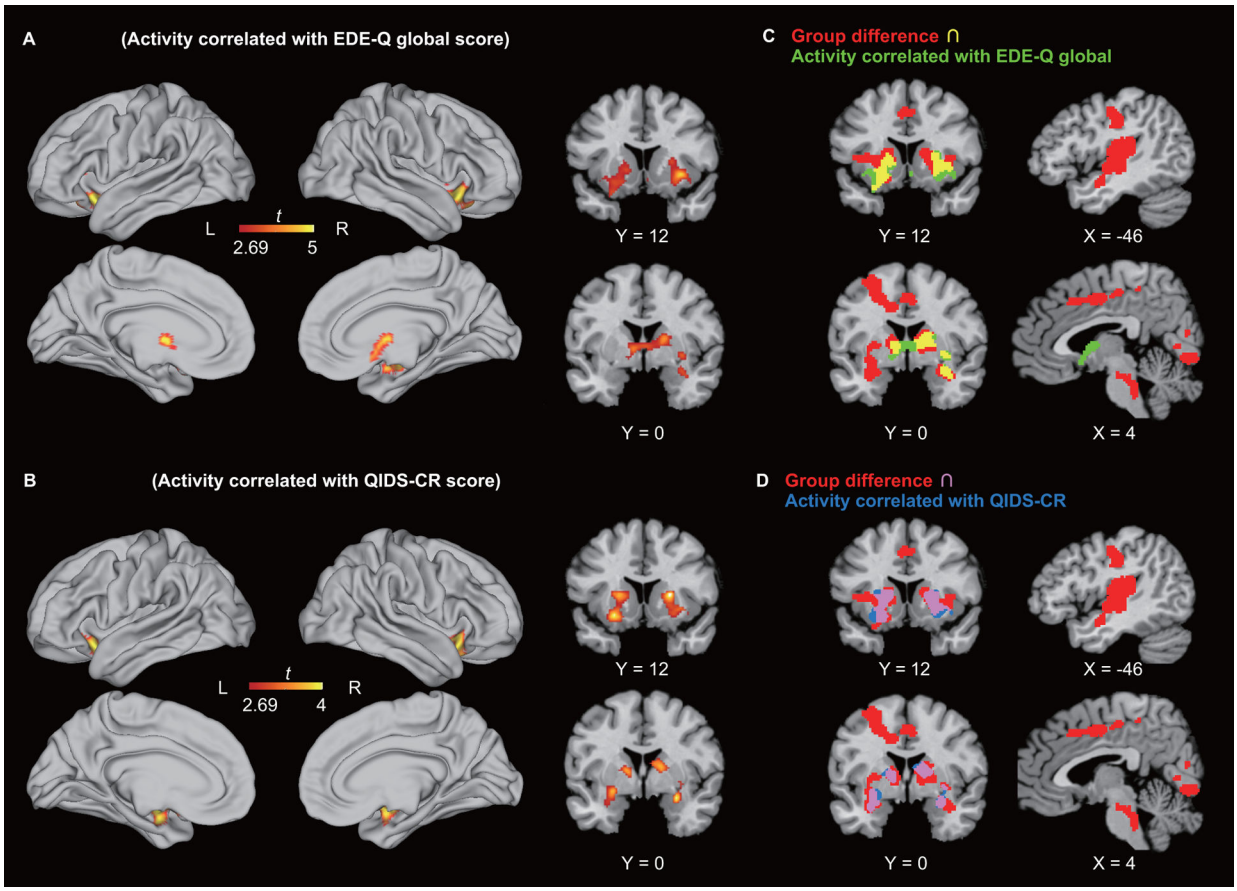

Figure 3.

Brain responses associated with symptom severity of eating disorder and depression. **A**. The responses to negative reciprocity in right amygdala and bilateral dorsal striatum were positively correlated with Eating Disorder Examination Questionnaire (EDE-Q) global score, independent of group. **B**. The responses to negative reciprocity in bilateral amygdala and dorsal striatum were positively correlated with Quick Inventory of Depression, Clinician-Rated (QIDS-CR) score, independent of group. **C**. Overlap (yellow) between areas respond differently between group to negative reciprocity (red) and those covary with EDE-Q global score (green). **D**. Overlap (purple) between areas respond differently between group to negative reciprocity (red) and those covary with QIDS-CR score (blue).

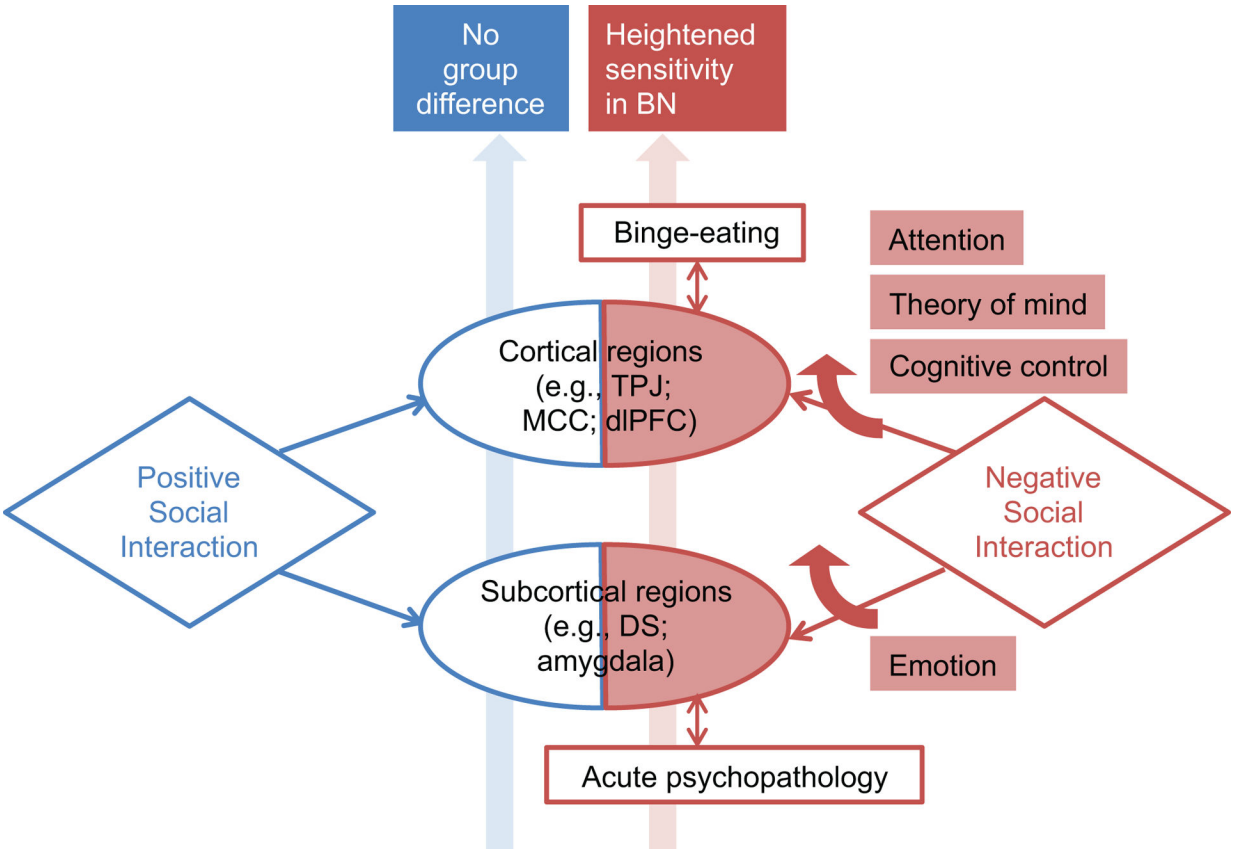

Figure 4.

A model for altered behavioral and brain responses to social interactions in bulimia nervosa. While no group difference was found between of bulimia nervosa (BN) and healthy comparison women (HC) in positive social interactions, BN showed both behavioral and neural evidence for a heightened sensitivity to negative interactions than HC. Negative social interactions induced elevated activations in cortical regions associated with attention, theory of mind, and cognitive control, as well as increased responses in subcortical regions related to emotion processing. The activation in intraparietal sulcus was associated with binge-eating frequency, while subcortical activations were positively correlated with acute psychopathology, including depression and overall eating disorder symptoms assessed at the time of the scan. TPJ, temporoparietal junction; dlPFC, dorsolateral prefrontal cortex; MCC, middle cingulate cortex; DS, dorsal striatum.

Table 1.

Demographic information and self-reported assessments

	BN		HC		Group difference (BN vs. HC)				
	mean	**SD**	**mean**	**SD**	***t***	***df***	***p***	***lower CI***	***upper CI***
Age (months)	348.4	72.2	316.4	53.7	1.79	48	0.080	−4.01	68.00
BMI	26.2	6.1	25.7	5.5	0.30	48	0.768	−2.82	3.79
IQ	118.4	11.6	118.0	13.5	0.10	47	0.917	−6.88	7.64
EDE-Q									
Global	3.1	1.3	0.6	0.5	8.56	29[a]	< 0.001	1.91	3.12
Restraint	2.1	1.6	0.4	0.6	4.80	27[a]	< 0.001	0.99	2.48
Eating concern	1.9	1.3	0.1	0.2	6.86	23[a]	< 0.001	1.28	2.38
Shape concern	4.0	1.6	0.9	0.9	8.29	34[a]	< 0.001	2.34	3.86
Weight concern	3.7	1.7	0.7	0.7	8.02	29[a]	< 0.001	2.23	3.76
Depression (QIDS-CR)	6.2	3.2	1.7	2.1	5.80	39[a]	< 0.001	2.92	6.04
Anxiety (SIGH-A)	10.1	5.8	2.3	2.7	6.01	32[a]	< 0.001	5.14	10.42
IPSAQ									
EB	−1.0	5.9	3.3	4.0	−2.95	44	0.005	−7.25	−1.37
PPB	0.5	0.3	0.5	0.3	−0.43	44	0.667	−0.21	0.14
NPB	0.5	0.3	0.5	0.2	−0.01	42	0.996	−0.16	0.16
Reward Sensitivity	11.8	3.4	9.0	3.4	2.81	44	0.007	0.80	4.88
Punishment Sensitivity	15.4	5.0	9.3	5.9	3.71	44	0.001	2.77	9.39

BN, bulimia nervosa; HC, healthy comparison women; SD, standard deviation; df, degrees of freedom; CI, 95% confidence interval. BMI, body mass index; IQ, Intelligence quotient assessed by Wechsler Adult Scale Intelligence (WASI); EDE-Q, Eating Disorder Examination Questionnaire; QIDS-CR, Quick Inventory of Depression, Clinician-Rated; SIGH-A, Structured Interview Guide for Hamilton Anxiety; IPSAQ, Internal Personal Situational Attributions Questionnaire; EB, externalizing bias; PPB, positive personalizing bias; NPB, negative personalizing bias.

[a]Degrees of freedom were adjusted because equal variance assumption was violated.