Neural Responses to Kindness and Malevolence Differ in Illness and Recovery in Women With Anorexia Nervosa

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Abstract: In anorexia nervosa, problems with social relationships contribute to illness, and improvements in social support are associated with recovery. Using the multiround trust game and 3T MRI, we compare neural responses in a social relationship in three groups of women: women with anorexia nervosa, women in long-term weight recovery from anorexia nervosa, and healthy comparison women. Surrogate markers related to social signals in the game were computed each round to assess whether the relationship was improving (benevolence) or deteriorating (malevolence) for each subject. Compared with healthy women, neural responses to benevolence were diminished in the precuneus and right angular gyrus in both currently-ill and weight-recovered subjects with anorexia, but neural responses to malevolence differed in the left fusiform only in currently-ill subjects. Next, using a whole-brain regression, we identified an office assessment, the positive personalizing bias, that was inversely correlated with neural activity in the occipital lobe, the precuneus and posterior cingulate, the bilateral temporoparietal junctions, and dorsal anterior cingulate, during benevolence for all groups of subjects. The positive personalizing bias is a self-report measure that assesses the degree with which a person attributes positive experiences to other people. These data suggest that problems in perceiving kindness may be a consistent trait related to the development of anorexia nervosa, whereas recognizing malevolence may be related to recovery. Future work on social brain function, in both healthy and psychiatric populations, should consider positive personalizing biases as a possible marker of neural differences related to kindness perception. *Hum Brain Mapp 00:000–000, 2015.*

Key words: eating disorders; social cognition; fMRI; neuroeconomic; default mode network

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INTRODUCTION

In anorexia nervosa, both biological and sociocultural factors contribute to the development of distorted cognitions and behaviors surrounding eating, weight, and shape, resulting in an illness characterized by dangerous weight loss [Becker, 2004; Bulik et al., 2007; Herpertz-Dahlmann et al., 2011; Kaye et al., 2011]. The focus of treatment in anorexia nervosa is weight-restoration, but more than half of patients relapse even after treatment leading to acute weight-recovery [Keel and Brown, 2010; Steinhausen, 2002]. Identification of intermediate phenotypes, specific biological characteristics that contribute to but alone do not cause a disease [Flint et al., 2014], may lead to a mechanistic understanding of anorexia nervosa. Here, we examined neural components of social behavior in anorexia nervosa, to assess whether biological trait differences in social behavior contribute to illness and recovery.

Problems related to social interaction, difficulties responding to social stressors, and an impaired quality of social life are observed in anorexia nervosa [Harrison et al., 2014; Troop et al., 2014; Troop and Treasure, 1997]. Neuropsychological studies have found differences in understanding other people's behaviors and emotions in both ill and recovered patients with anorexia nervosa [Harrison et al., 2014; Tchanturia et al., 2013], and reduced neural activity has been reported in MRI tasks using social stimuli in patients with anorexia nervosa [McAdams and Krawczyk, 2011, 2014; Schulte-Ruther et al., 2012]. These preliminary studies suggested that biological differences related to social relationships might be involved in both disease and recovery from anorexia nervosa.

We chose a multiround trust game to probe both behavioral and neural components related to understanding other people's behavior (Fig. 1). Within the trust game, a relationship develops, constrained by game rules, allowing discrete windows into the computational processes that occur in the brain in response to social signals [Kishida et al., 2010]. Most importantly, human social behavior is about relationships between people, and the delivery of all empirically-validated treatments for anorexia nervosa, in addition to nutritional support, include interactions between people, either the therapist and the patient or the patient and their family [Berkman et al., 2006; Lock, 2010]. The multiround trust game allows comparisons of both the neural responses to one's own behavior and others [Tomlin et al., 2006].

We designed our study to examine behavioral and neural differences related to social interaction in three groups of subjects: healthy women, women currently with anorexia nervosa, and women in long-term weight-recovery following anorexia nervosa. The multiround trust game allows simultaneous collection of behavioral and neural data that can be examined in the context of positive and negative interactions during the game. The primary analyses here involved group comparisons of the behavioral and neural differences related to positive and negative interactions in the game. The goal was to identify differences related to the trait of anorexia (present in both ill and weight-recovered) and the state of anorexia (present only in ill). First, we hypothesized that women currently with anorexia nervosa, but not those in recovery, would show reduced sensitivity, both behaviorally and neurally, to the other person's behavior during the game. Secondarily, we hypothesized that attribution biases, a cognitive measurement related to one's expectations about other people, would be correlated with neural activations in response to positive and negative interactions with their partner during the trust game.

METHODS

Participants

A total of 63 female participants, between 18 and 47 years of age, were recruited for this study using flyers and advertisements at UT Southwestern as well as referrals from clinical providers in the Dallas area. The participant groups consisted of 21 healthy controls (HC), 23 individuals with a recent history of anorexia nervosa (AN-C), and 19 individuals with sustained weight recovery after having had anorexia nervosa (AN-WR). The study was approved by the institutional review board at the University of Texas at Southwestern Medical Center, and subjects provided written informed consent at the first visit.

Subjects were interviewed using the Structured Clinical Interview for DSM-IV disorders (SCID-RV) to confirm the diagnosis of anorexia nervosa in the AN-C and AN-WR groups, and the absence of current or past eating disorders in the HC group. All subjects in the AN-C group met DSM-IV criteria for anorexia nervosa within the previous 12 months. Most of these subjects (16 of 23) were scanned within 3 months of completing an intensive eating disorder program (resulting in some patients having a normalized weight at the scan); the others were in outpatient treatment, but had also maintained a stable weight, albeit below normal (BMI $<$ 18.0) for at least 2 months before the scan. These criteria were selected to minimize effects of acute weight loss on brain function, but to still allow examination of patients in the process of obtaining treatment for this disease.

All subjects in the AN-WR group had met DSM-IV criteria for anorexia nervosa previously in their life but had maintained a healthy weight, defined as a BMI greater than 19.0, for at least 2 years, and had resumed menstrual cycles. None of the subjects in the AN-WR group had been treated in an inpatient, partial hospital or residential eating disorder program for at least 2 years. These subjects were recruited through on-campus flyers, referrals from outpatient clinical providers, and postings on eating disorder advocacy and support sites.

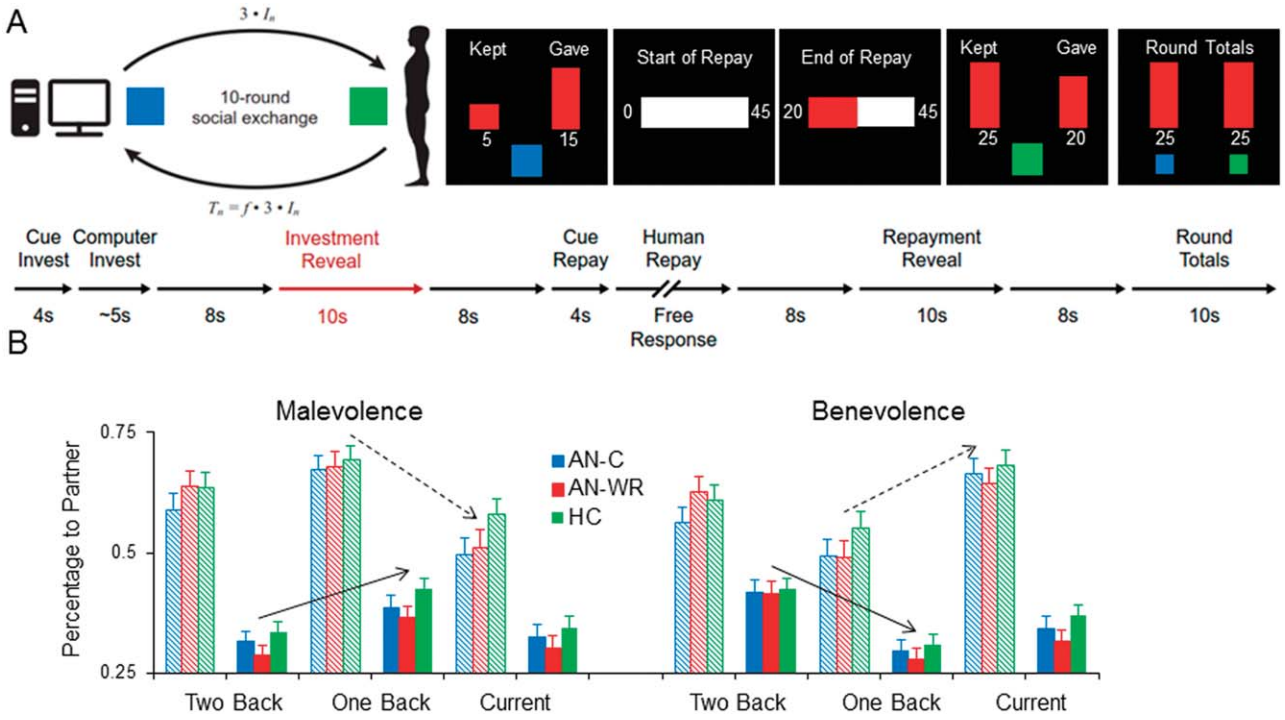

Figure 1.

Schematic of the trust game and a demonstration of the behavioral definition of malevolence and benevolence. **A**. The trust game is a social interaction paradigm with 10 rounds of interactive behaviors between the computer-simulated investor (receiving 20 points and investing I_n) and our subject, the trustee (receiving $3\times$ I_n and repaying T_n). During a round, the timeline of task events is shown along the bottom, with on-screen images shown for the investment reveal, start and end of the repay period, repay reveal, and round totals screens along the upper right. The screen was blank during the computer invest and delay periods. During repay, subjects began with a blank white bar, extending from 0 to 3 times the investment (Start of Repay). Subjects used a button box to increase or decrease then submit payment (End of Repay), when the red portion corresponded to the repayment. The repayment was shown to the subject using the same format as the invest reveal, followed by round totals. **B**. Responses were sorted based on whether malevolence or benevolence had occurred during the prior two rounds. The percent of the trustee's repay is shown with solid bars and the computer-partner's percent of investment is shown in dashed columns, averaged for each group of subjects. During a malevolent round, the repayment fraction increased (upward black arrow), but the investment fraction (downward dashed arrow) decreased. During a benevolent round, the repayment fraction decreased (downward black arrow), but the investment increased (upward dashed arrow).

None of the subjects in either the AN-C or the AN-WR groups had met the DSM IV criteria for bulimia nervosa for at least 12 months, although six subjects in each clinical group had met DSM IV criteria for bulimia nervosa in their lifetime. Subjects with lifetime diagnoses of bipolar disorders, psychotic disorders, and substance dependence were excluded, as were subjects with substance abuse during the prior 12 months. None of the subjects had met criteria for a major depressive episode in the month before the scan, but a few subjects had met criteria for recurrent major depressive disorder in their lifetime (four AN-C, five AN-WR). Some subjects had met criteria for an anxiety disorder before the development of anorexia nervosa (anxiety not otherwise specified (three AN-C, three AN-WR) and generalized anxiety disorder (three AN-C, three AN-WR)). Subjects on antidepressant medications were permitted if their medication dose had not changed during the month before the scan (13 AN-C and 8 AN-WR on antidepressant medication).

Assessments

The Wechsler Abbreviated Scale of Intelligence (WASI) was administered to provide an estimate of intelligence quotient. Clinician-administered quantitative assessments of depression (Quick Inventory of Depression, Clinician-Report), and anxiety (Structured Inventory of Generalized Hamilton Anxiety Symptoms, SIGH-A) were obtained at the initial appointment. The Eating Attitudes Test-26

TABLE I. Participant characteristics

	Group, mean (SD)			Group differences	
	HC (n = 21)	AN-C (n = 23)	AN-WR (n = 19)	$F_{2,61}$	p
Age (yrs)	27.0 (6.1)	26.3 (8.1)	29.6 (8.3)	1.29	0.282
ED onset age (yrs)	—	16.3 (6.8)	14.0 (3.6)	1.89	0.177
Intelligence quotient (WASI)	122.7 (8.5)	118.7 (8.8)	118.3 (13.8)	1.01	0.369
Current body mass index	22.8 (2.7)	18.0 (1.5)	22.8 (2.7)	31.65	<0.001*†
Eating Attitudes Test (EAT)	3.1 (3.7)	35.6 (18.5)	15.9 (9.6)	40.46	<0.001*†‡
Depression (QIDS-CR)	1.5 (2.0)	6.3 (5.7)	5.0 (4.3)	7.70	0.001*†
Anxiety (SIGH-A)	2.0 (2.6)	10.0 (8.7)	8.1 (6.5)	9.54	<0.001*†
EDE-Q					
Global	—	3.93 (1.38)	2.12 (1.38)	4.29§	<0.001
Restraint	—	4.06 (1.31)	1.89 (1.41)	5.13§	<0.001
Eating concern		3.30(1.77)	1.35(1.00)	3.98§	<0.001
Shape concern	—	4.69 (1.47)	2.81 (1.60)	3.92§	<0.001
Weight concern	—	3.74 (1.60)	2.93 (1.78)	1.62§	0.114
IPSAQ					
Externalizing bias	4.3 (4.0)	−2.8 (6.3)	1.5 (4.6)	9.18	<0.001*‡
Negative personalizing bias	0.6 (0.2)	0.6 (0.4)	0.7 (0.2)	0.61	0.546
Positive personalizing bias	0.4 (0.3)	0.6 (0.3)	0.5 (0.3)	0.62	0.544
Positive Internal	8.6 (2.7)	6.7 (3.3)	8.2(2.7)	2.38	0.101
Positive personal	3.2 (2.3)	5.4 (3.8)	3.8 (3.2)	2.21	0.119
Positive situational	4.1 (2.3)	3.9 (3.2)	3.9 (2.4)	0.01	0.999
Negative internal	4.3 (2.4)	9.5 (4.4)	6.6 (3.9)	9.13	<0.001*‡
Negative personal	6.7 (3.1)	3.5 (2.7)	6.2 (2.8)	7.23	0.002*‡
Negative situational	4.9 (2.8)	3.0 (3.5)	3.2 (3.0)	2.42	0.097

HC, healthy comparison women; AN-C, women with anorexia nervosa; AN-WR, women in weight recovery after anorexia nervosa. ED, Eating Disorder; WASI, Wechsler Adult Scale Intelligence; EAT, Eating Attitudes Test, QIDS-CR, Quick Inventory of Depression, Clinician-Rated; SIGH-A, Structured Interview Guide for Hamilton Anxiety; EDE-Q, Eating Disorder Examination Questionnaire; IPSAQ, Internal Personal Situational Attributions Questionnaire.

Post hoc statistical comparisons were performed using Bonferroni correction: *AN-C differ significantly from HC ($P < 0.05$); †AN-WR differ significantly from HC ($P < 0.05$); ‡AN-C differ significantly from AN-WR ($P < 0.05$); §t-value for the comparison of AN-C and AN-WR ($P < 0.05$).

measured eating behaviors in all three groups; the Eating Disorder Examination Questionnaire was also given to subjects in the AN-C and AN-WR groups (Table I, Demographic & Clinical Assessments). The Internal, Personal, and Situational Attribution Questionnaire (IPSAQ) is a self-report assessment that was completed by all participants [Kinderman and Bentall, 1996; Kinderman et al., 1998].

Statistical Analysis of Demographic and Clinical Data

All demographic and clinical comparisons were conducted in SPSS (SPSS, Inc., Chicago). Measures that were obtained for all three subject groups (age, BMI, WASI, QIDS, SIGH-A, IPSAQ) were compared using analysis of variance (ANOVA) with post hoc Bonferroni comparisons, with $P < 0.05$ as the statistical criterion. Measures collected only from the AN-C and AN-WR groups (EDE-Q, age of onset) were compared with a two-sample t-test, also using $P < 0.05$ as the criterion for significance.

Neuroimaging Task Design

The Trust Game is a multiround, two-party exchange game based on the idea of investing money with a person managing a stock market [King-Casas et al., 2005; Tomlin et al., 2006]. One party, in this case a computer-simulation of a healthy human, was given the role of investor, while our subject played the role of trustee of the account (Fig. 1). All subjects were told that they were playing a subject in the same building over the internal network, to facilitate a belief of interaction with a real person.

Behavioral Analysis of Trust Game

The game includes 10 offers from the simulated partner and 10 responses by the subject. Behavioral data from the game were analyzed in two ways. First, the overall earnings of each subject and also their simulated partner, summed across the ten rounds, were compared across the three groups using analysis of variance (ANOVA), with post hoc Bonferroni comparisons in SPSS (threshold,

$P < 0.05$). Second, previous work has identified the amount and type of reciprocity occurring in the game to be the most significant determinant of future changes in investment [King-Casas et al., 2005]. Reciprocity is defined as the change in investment relative to the change in return $(I_n - I_{n-1}) - (T_{n-1} - T_{n-2})$, where n is the current round of the game and can be computed for each round of play for rounds 2 through 10. Using a standard multiple regression, correlation coefficients between the trustee's change in response $(T_n - T_{n-1})$ and the reciprocity experienced by the trustee $((I_n - I_{n-1}) - (T_{n-1} - T_{n-2}))$ were determined for each group. Reciprocity was also considered based on its polarity, where positive reciprocity refers to an improving relationship for the trustee relative to the investor (the experience of benevolence) and negative reciprocity reflects a worsening relationship for the trustee relative to the investor (the experience of malevolence). Group differences in the reciprocity correlation coefficients (overall, positive, and negative) were assessed using a multiple regression followed by pairwise comparisons in matlab ($P < 0.05$).

MRI Acquisition and Analysis

All images were acquired with a 3T Philips MRI scanner. Anatomical imaging used an MPRage sequence to acquire high resolution, T1-weighted images of the whole head using a $TR = 2{,}100$ ms, $TE = 3.7$ ms; slice thickness of 1mm with no gap, a 12° flip angle, and 1 mm^3 voxels. Functional images utilized a 1-shot gradient T2*-weighted echoplanar (EPI) image sequence with a repetition time (TR) of 2,000 ms, a flip angle of 90°, a 220 mm field of view, with a 64 × 64 pixel image matrix for measurement of the blood oxygenation level-dependent (BOLD) effect. Echo time (TE) was 25 ms and 37 slices, parallel to the anterior-posterior commissural line, were collected (4 mm, no gap). The resulting functional image voxels had dimensions of 3.4 × 3.4 × 4.0 mm. Padding minimized head movement during image acquisition. Subjects viewed visual stimuli during the functional scans on a rear-projection screen using an angled mirror attached to the head coil and provided responses using a three-key fiber-optic button box.

The fMRI data were analyzed separately using the same preprocessing methods for both tasks using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Images were slice-timing corrected and realigned to the first volume within subject. The anatomical image was co-registered to the mean of the functional images, and segmented and normalized to the standard MNI template. The realigned functional images were then normalized to the MNI template, and smoothed using a Gaussian kernel, 8 mm full width half maximum (FWHM). The voxel time series were high-pass filtered (128 s).

For each subject, data were analyzed using the massively univariate SPM approach to generate individual design matrices (see Supporting Information for full matrix). β-maps were extracted from the GLM analysis for the regressors of interest, to create single-subject one-sample t-test contrast images that were combined for group map analyses. Task regressors of interest included the investor reveal and the submission of the repayment [Tomlin et al., 2006]. A second GLM was created based on reciprocity, using regressors for benevolence or malevolence based on whether the current investor behavior towards the trustee showed reciprocity below or above the median reciprocity (within subject) [King-Casas et al., 2005], and adding an event investor reveal for the first two reveals before reciprocity was established (Fig. 1B). Overall neural activations for each task regressor for each participant population were examined using a voxel height of $P_{FWE} < 0.05$, and an extent of five voxels (231 mm^3).

The second-level whole brain analyses are the focus of the manuscript. Two types of second level analyses were conducted, with age included as a nuisance covariate. First, a whole brain voxel-wise ANOVA with post hoc t-tests identified regions of interest (ROIs) that differed across the three groups, for each of the task regressors described above. Statistical criterion was set to a cluster-level $P_{FWE} < 0.05$, using an initial voxel-wise $P < 0.005$, and the resulting minimal cluster sizes ranged from 105 to 111 voxels. Second, whole-brain regressions related the first-level images for benevolence and malevolence with both clinical (QIDS, SIGH-A, EAT) and psychological (EB, PPB, NPB) measures, using an initial voxel-wise $P < 0.001$, with extent corresponding to a cluster $P_{FWE} < 0.05$.

ROIs obtained from both second level analyses, the ANOVAs for malevolence and benevolence, as well as the whole-brain regressions, were further examined by extracting the average β value within each cluster for each subject using the MarsBar toolbox (sourceforge.net/projects/marsbar). These β values were transferred to SPSS (SPSS, Inc., Chicago) for ANOVA with post hoc Bonferroni comparisons ($P < 0.05$) to determine the presence and directionality of group differences and their effect sizes. Finally, linear regressions examined whether the clinical variables (QIDS, SIGH-A, and EAT) also correlated with extracted β values in these ROIs.

Effects of Medications

Potential differences in all ROI activations related to the use of psychoactive medications were considered in a group × medication ANOVA, excluding the healthy subjects to determine if there were group, medication, or interactions between group and medication. For each individual subject, neural activations within each of the ROIs obtained from the whole-brain group ANOVAs for the benevolence and malevolence task periods were extracted as individual β values. A 2 × 2 ANOVA was then performed, containing the β values factored by both group and medication status. In that way, the neural activity

within each ROIs was assessed for differences related to clinical group (AN-C vs. AN-WR), medication use (on an antidepressant or not), and for the interaction of group and medication, setting a pre-existing threshold for significant differences set at $P < 0.05$.

RESULTS

Scale Measures

The three groups of subjects did not differ in age or intelligence (WASI) but did differ in that more pronounced clinical eating disorder symptoms (EAT) and a lower body mass index (BMI) were present in the AN-C group compared with the other two groups (Table I). Both the AN-WR and AN-C groups showed similar levels of anxiety (SIGH-A) and depression (QIDS-CR), and more than the HC group (Table I). The AN-WR group showed less eating disorder symptomatology than the AN-C group (both on the EAT and the EDE-Q and all subscales save EDE-Q-weight) and more eating disorder symptoms than the HC group (EAT) (Table I).

Several differences were observed in the two clinical groups using the IPSAQ (Table I). This scale involves the explaining the reasoning for various hypothetical positive ("A friend gave you a ride home") and negative ("A friend talked behind your back") social interactions, and provided three attribution bias measures: the externalizing bias (EB): the difference in attributing responsible for positive events rather than negative events to oneself; the positive personalizing bias (PPB), the times the subject identified the friend as responsible for a positive interaction divided by the times attributing responsibility to the situation; and the negative personalizing bias (NPB), the times the subjects attributed responsibility to the friend for a negative interaction relative to the situation. The AN-C group had a significantly lower EB and higher overall Negative Internal Attributions and lower Negative Personal Attributions compared with both the AN-WR and HC groups (Table I). There were no differences in the PPB or NPB across the three groups.

Behavioral Data From the Trust Game

The Trust Game yields behavioral data related to the earnings of each player and their simulated partner as well as information about the amount and type of reciprocity developing in the relationship (Fig. 1, Supporting Information Table SI). First, there were no differences in the overall earnings of points during the game by group for either the computer-simulated investor (computer, HC 229, AN-C, 228; AN-WR 209, $F = 0.62$, $P = 0.54$) or the trustees (subject, HC, 215, AN-C, 200; AN-WR 228, $F = 0.95$, $P = 0.39$). Reciprocity is a measure of the change in investment relative to the change in return $(I_n - I_{n-1}) - (T_{n-1} - T_{n-2})$, where n is the current round of the game [King-Casas et al., 2005]. For all three groups, reciprocity was predictive of subsequent investments (reciprocity correlation coefficients, HC 0.31, AN-C 0.20, AN-WR 0.11; $F = 15.9$, $P < 0.001$), but there were significant group differences in the reciprocity correlation coefficients ($F = 4.1$, $P = 0.01$), with the most reciprocity observed in the HC group (Supporting Information Fig. S1).

The valence of reciprocity was considered, using the calculation described in King-Casas [King-Casas et al., 2005], and illustrated graphically as the averaged percent change occurring in investment and return that occur over the course of three rounds of the game in Figure 1B. Benevolence, or positive reciprocity, was defined as the investor providing a higher percentage of funds relative to the percentage increase or decrease in funds given by the trustee. Malevolence, or negative reciprocity, was defined as the investor providing a smaller percentage of funds relative to the trustee's percentage change. In Figure 1B, the percentage of money given to the subject (averaged for all trials with that type of reciprocity for each group) for a current malevolent round (left) and a current benevolent (right) round are shown, accompanied by the averaged percentages for the two preceding rounds. There were not significant group differences in the aggregate percentage changes as illustrated here. However, using a multiple regression to assess the relationship between positive and negative reciprocity and subsequent investments, we found that there were significant group differences related to the malevolence regression coefficients (HC -0.39, AN-C -0.26, AN-WR, -0.13, $F = 3.59$, $P = 0.03$), with the pairwise comparison demonstrating reduced responsivity for the AN-WR group relative to the HC group ($t = 2.6$, $P = 0.008$). We did not observe significant group difference related to the benevolence regression coefficients (HC 0.24, AN-C 0.14, AN-WR 0.07, $F = 1.37$, $P = 0.26$). No significant differences were seen in the average number of rounds displaying benevolence (mean benevolent rounds per subject by group, HC 3.9, AN-C 4.0, AN-WR, 3.4, $F = 2.86$, $P = 0.07$) or malevolence (mean malevolent rounds per subject by group, HC 3.8, AN-C 3.4, AN-WR 3.8, $F = 0.77$, $P = 0.47$).

Neural Responses to Benevolence and Malevolence

β-images related to the neural responses occurring during the investment reveal period, sorted by malevolence and benevolence, are the focus of this manuscript (see Fig. 1). The overall neural activations observed for benevolent and malevolent interactions for each group separately are displayed in Figure 2A (see also Supporting Information Fig. S2, Tables S2, S3). For both the HC and AN-WR, the neural responses in the case of both benevolence (yellow) and malevolence (red) are similar, leading to a preponderance of orange. Both groups have large clusters of neural responses extending throughout the occipital, parietal and

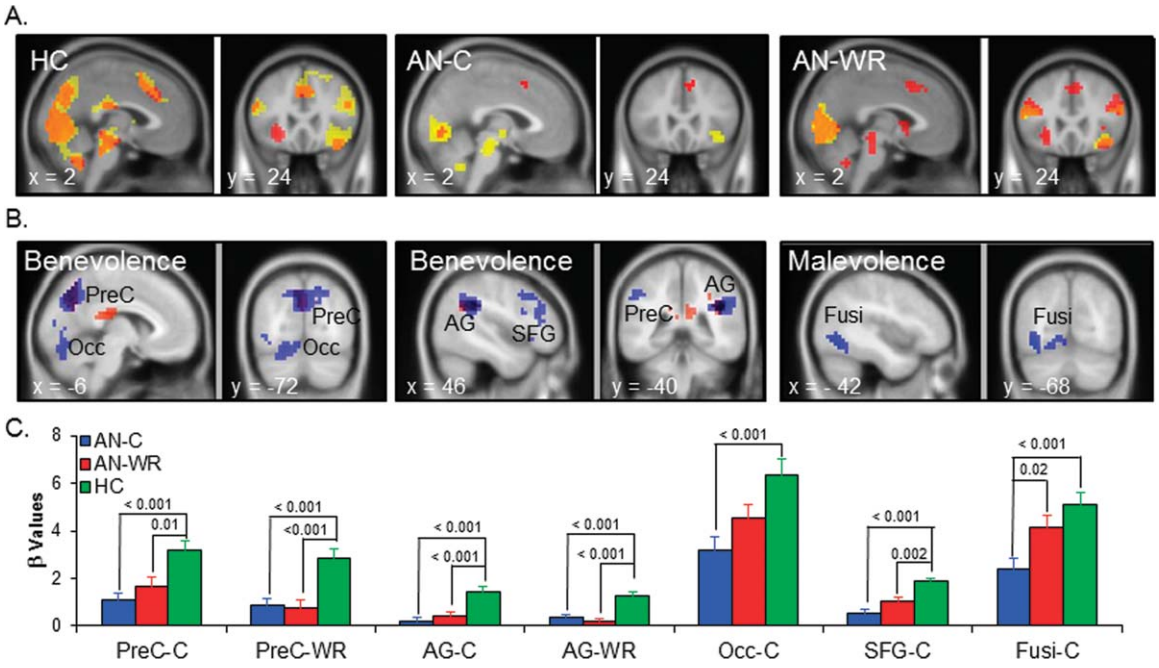

Figure 2.

A. Group maps of midline and frontal neural responses after receiving benevolent (yellow) or malevolent (red) investments from the partner are displayed for each group, using a voxel height threshold of $P_{FWE} < 0.05$ with a minimum cluster size of five voxels, corresponding to a cluster-level corrected threshold of $P_{FWE} < 0.005$. **B**. Clusters identified from the pairwise comparisons for the HC-AN-C contrast are displayed in blue and the HC-AN-WR contrast in red (threshold, cluster $P_{FWE} < 0.05$). **C**. β values were extracted from each ROI, and *P* values are above brackets are provided for the significant post hoc pairwise differences. PreC: precuneus; AG, angular gyrus, Occ, occipital, SFG, superior frontal gyrus; Fusi, fusiform; -C, cluster obtained from HC-AN-C contrast (blue areas in 2B); -R, cluster obtained from HC-AN-WR contrast (red areas in 2B).

temporal regions during both benevolent and malevolent interactions, as well as bilateral clusters in the superior, middle and inferior frontal gyri. The AN-C group has fewer and smaller clusters during both benevolent and malevolent interactions (Supporting Information Tables S2 and S3).

Several neural regions showed differences related to benevolence and malevolence in the whole-brain ANOVA comparing the three groups (Table II, Fig. 2B,C). During benevolence, both groups with anorexia nervosa (AN-C and AN-WR) showed reduced activation of clusters in the precuneus (PreC-C, PreC-WR) and the right angular gyrus (AG-C, AG-WR) relative to the HC group. Additionally, the AN-C group had less activity in an occipital cluster (Occ-C) and the superior frontal gyrus (SFG-C) relative to the HC group. During malevolence, the AN-C group also had reduced activation of a left fusiform cluster (Fusi-C) relative to the HC group. Of note, there were no differences in pairwise comparisons of the AN-WR and HC groups during malevolence, only benevolence. Examination of the extracted β values within these regions showed elevated activity in the HC group compared with both the AN-C and AN-WR groups in all regions except the Occ-C and the Fusi-C. The Fusi-C cluster showed reduced activity in the AN-C group relative to both the AN-WR and HC groups (Table II); the Occ-C only showed a significant difference with reduced activity in the AN-C group relative to the HC group. Medication status of the AN-C and AN-WR participants did not significantly alter the β values in the benevolence or malevolence ROIs, using a Group by Medication ANOVA to compare the extracted β values in the benevolence and malevolence ROIs (Supporting Information Table S4).

Positive Personalizing Bias and Benevolence

Separate, whole-brain regression analyses were utilized to assess whether responses to benevolent or malevolent interactions could be related to the subject's clinical or psychological characteristics, including depression (QIDS), anxiety (SIGH-A), eating disorder symptoms (EAT), and attribution biases (PPB, NPB, EB). In sum, a total of 12 regressions were examined: only one resulted in any clusters meeting the a priori significance threshold (cluster $P_{FWE} < 0.05$). The positive personalizing bias (PPB) of the

TABLE II. Regions of interest from whole-brain group ANOVA and regressions[a]

	Neural ROI characteristics						β values by group, mean (SD)			Group comparisons		
	Volume			MNI coordinates								
Condition and region	(mm^3)	Clustersize	Peak Z	x	y	z	AN-C	AN-WR	HC	F	P	Effect size
Benevolence Clusters, ANOVA												
Main effect of group												
Left precuneus	5,775	125	3.68	−6	−72	42	1.18(1.9)	1.64(2.1)	4.20(2.7)	17.4	<0.001*†	0.54*, 0.47†
HC-AN-C												
Right angular gyrus (AG-C)	7,669	166	4.58	46	−40	30	0.20(0.7)	0.41(0.7)	1.43(0.9)	24.4	<0.001*†	0.60*,0.53†
Right superior frontal gyrus (SFG-C)	11,596	251	4.23	22	20	54	0.53(0.9)	1.02(0.8)	1.86(0.6)	28.9	<0.001*	0.66*, 0.51†
Left precuneus (PreC-C)	23,793	515	4.09	−6	−72	42	1.11(1.3)	1.68(1.6)	3.20(1.8)	17.3	<0.001*†	0.55*, 0.41†
Right occipital gyrus (Occ-C)	8,547	185	3.91	−38	−80	−6	3.19(2.6)	4.56(2.5)	6.35(3.2)	13.8	<0.001*	0.48*
HC-AN-WR												
Right angular gyrus (AG-WR)	5,729	124	4.36	30	−28	34	0.37(0.5)	0.17(0.6)	1.25(0.7)	16.9	<0.001*†	0.59*,0.64†
Left precuneus (PreC-WR)	8,455	183	4.07	−6	−72	34	0.89(1.3)	0.76(1.4)	2.84(1.9)	14.6	<0.001*†	0.51*,0.53†
Malevolence clusters, ANOVA												
HC-AN-C												
Left fusiform gyrus (Fusi-C)	12,151	263	3.97	−42	−68	−10	2.39(2.3)	4.12(2.2)	5.09(2.4)	14.4	<0.001*‡	0.50*, 0.36‡
Positive personalizing bias clusters, regression												
Precuneus/posterior cingulate (PC)	20,559	445	4.93	6	−60	34	3.50(2.5)	4.97(2.6)	5.67(2.7)	7.4	0.009*	0.38*
Occipital, lingual, calcarine (Occ)	22,407	485	4.26	6	−64	−10	0.56(0.8)	0.50(1.0)	1.18(1.3)	3.3	0.075	ns
Right temporoparietal junction (RTPJ)	5,174	112	4.65	42	−60	30	0.91(1.3)	1.21(1.5)	2.63(1.8)	12.6	<0.001*†	0.48*, 0.40†
Left temporoparietal junction (LTPJ)	1,987	43	4.12	−38	−68	22	0.88(1.2)	0.69(1.2)	1.75(0.9)	5.7	0.02*†	0.38*, 0.45†
Dorsal anterior cingulate (dACC)	2,633	57	4.18	6	44	46	0.40(0.9)	0.99(1.3)	1.46(1.1)	9.5	0.003*	0.47*

[a]Cluster-level correction to $P_{FWE} < 0.05$. The volume of each voxel is 46.2 mm^3. Peak Z score is at the MNI coordinates for the specified anatomical location. HC, healthy comparison women, AN-C, currently-ill women with anorexia, and AN-WR, weight-recovered women with anorexia. Missing comparisons did not have any clusters at threshold. Effect sizes computed from Cohen's d.

*AN-C differ significantly from HC ($P < 0.05$); †AN-WR differ significantly from HC ($P < 0.05$); ‡AN-C differ significantly from AN-WR ($P < 0.05$).

IPSAQ, a measure obtained from a self-report assessment about the interpretation of positive social gestures, correlated with neural activations during benevolence (Fig. 3). This negative correlation was presented in all subjects, independent of group, between the β values extracted from the aggregate of these clusters and the PPB (Fig. 3A, $r = -0.58$, $P < 0.001$). Each of the three subject groups also showed a similar negative correlation between the PPB and neural activations in the aggregate of these clusters when examined independently (AN-C, $r = -0.61$, $P = 0.002$; AN-WR, $r = -0.61$, $P = 0.006$; HC, $r = -0.42$, $P = 0.06$). Supporting the specificity of this relationship, the PPB as well as the other biases from the IPSAQ (EB and NPB) did not yield any significant clusters during other task periods (investment reveal on malevolent rounds, trustee submission, and trustee reveal).

Each ROI obtained from the PPB regression was considered separately by extracting the β values from each ROI for each subject and conducting an ANOVA to compare activations across the groups (Table II, Fig. 3B,C). These ROIs included a cluster in the precuneus and posterior cingulate (PC), an occipital region including lingual, calcarine and fusiform gyri (Occ), the temporoparietal junctions (RTPJ; LTPJ), and the dorsal anterior cingulate (dACC). Both of the TPJ clusters showed group differences in the ANOVA (LTPJ $F = 5.70$, $P = 0.02$; RTPJ $F = 12.6$, $P < 0.001$), and on pairwise comparison significant differences were present with both the AN-C (LTPJ $t = 2.61$, $P = 0.013$; RTPJ $t = 3.57$, $P < 0.001$) and the AN-WR (LTPJ $t = 3.04$, $P = 0.004$; RTPJ $t = 2.63$, $P = 0.01$) groups showing less activity than the HC group. In contrast, although both the dACC ($F = 9.54$, $P = 0.003$) and the PreC ($F = 7.38$, $P = 0.009$) showed group differences, pairwise comparisons demonstrated that these differences resulted only from significantly reduced activity in the AN-C group relative to the HC group (dACC, $t = 3.36$, $P = 0.002$; PreC, $t = 2.71$, $P = 0.01$). No significant group differences were related to activations of the Occ cluster (Occ, $F = 3.27$, $P = 0.08$).

Clinical Symptoms and ROI

Although the clinical variables (QIDS, SIGH-A, and EAT) did not result in significant neural clusters in the whole-brain regressions, it was possible that the ROIs identified in the group analyses or the PPB regression might still be related to clinical symptoms in the patients. To consider this question, a tertiary analysis correlated the β values extracted from all ROIs (Table II) with the measures for depression, anxiety, and eating disorder behaviors amongst the clinical subjects. No significant correlations were identified (Supporting Information Table S5).

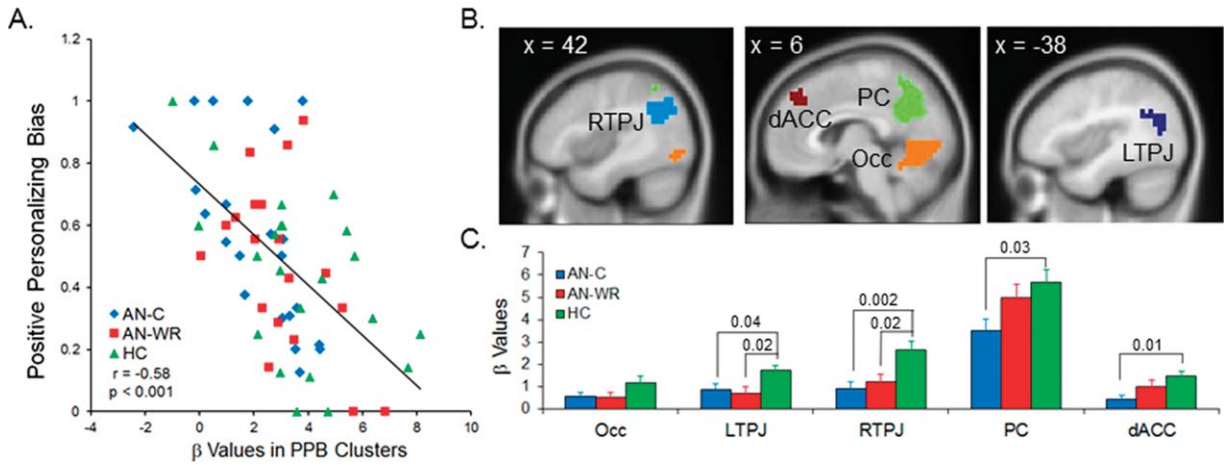

Figure 3.

Neural responses are related to the positive personalizing bias during benevolence in healthy women, women with anorexia nervosa, and women in recovery from anorexia nervosa. **A**. Each subject's average β value across all the PPB clusters is plotted against their PPB. All three groups demonstrate a similar relationship: lower PPB values correspond to more neural activations during benevolence. **B**. The positive personalizing bias, PPB, showed strong correlations with five different clusters during benevolence (occipital region (Occ), left temporoparietal junction (LTPJ), right temporoparietal junction (RTPJ), posterior cingulate and precuneus (PC), and dorsal anterior cingulate (dACC)). All clusters identified from the whole-brain regression of the PPB with neural activity during benevolent investor reveal periods, using a voxel height threshold of $P < 0.001$ and a cluster-level corrected threshold of $P_{FWE} < 0.05$. **C**. The average β-values within each cluster provided for each group. The P values and brackets in the column graphs correspond to the Bonferroni corrected P after post hoc pairwise comparisons, if initial ANOVA had shown a group effect ($P < 0.05$). Errors bars are standard error of the mean.

DISCUSSION

We show here that recovery from anorexia nervosa is associated with increased neural activity in several social cognitive regions when considering other people and their behaviors. Both groups with anorexia nervosa showed diminished neural responses in the precuneus (PreC-C, PreC-WR) and right angular gyrus (AG-C, AG-WR) to positive social gestures in the game relative to the HC, but only the AN-C group showed neural differences during negative social interactions, consisting of reduced activity in the left fusiform (Fusi-C) Fusi. Furthermore, a psychological scale measure, the PPB, correlated with neural activations in the PC, dACC, and bilateral TPJ during benevolence, suggesting a potential relationship between this cognitive attribution style and kindness perception.

Recovery and Illness in Anorexia Nervosa

The study objective was to determine if social interactive behaviors could be related to illness and recovery in anorexia nervosa. We found differences in the attribution measurements using the IPSAQ, behavioral differences in reciprocity in the trust game, and neural differences in response to benevolent and malevolent interactions. First, on the IPSAQ, the AN-C group had a negative externalizing bias and higher negative internalizing score, both measures that suggest increased self-blame, and a lower negative personalizing score, showing a reluctance to blame others for negative interactions, than both the HC and the AN-WR subjects. Second, the AN-C subjects showed reduced activation of the occipital and left fusiform gyri when experiencing malevolence. In contrast, the AN-WR subjects were less reactive to malevolence behavior from the opponent, showing neural activity similar to the HC subjects during malevolence. In sum, this data supports an idea that recovery is associated with increased neural processing of negative social interactions. One interpretation of these findings is that learned behavioral strategies related to responding to negative social interactions may facilitate recovery: thus the AN-WR group is more aware of negative social interactions (neural similarities with HC group) but responds less to malevolence than either the AN-C and HC groups (behaviorally less reactive to malevolence). The AN-C group appears less neurally aware of the negative social interactions (differs from AN-WR and HC). This interpretation suggests that there may be a period during recovery when patients become aware of malevolence but still react to it. Further work will be needed to better understand how recognition and reactivity to negative social experiences is important for recovery from this disease.

Both groups of patients showed reduced neural modulations to benevolence in several cortical regions, including the right angular gyrus (AG-C, AG-WR) and precuneus (PreC-C, PreC-WR). Prior studies have reported that grey matter volume in the cingulate and precuneus is reduced in patients with anorexia nervosa [Gaudio et al., 2011; McCormick et al., 2008; Muhlau et al., 2007]. The connectivity of the precuneus to the lateral prefrontal cortex differs in weight-recovered patients with anorexia nervosa [Cowdrey et al., 2014]. Using a verbal attribution task in which subjects were asked to evaluate themselves or a friend using a social adjective ("I believe I am kind" versus "I believe my friend is thoughtful"), McAdams and Krawcyzk previously reported reduced activation of the precuneus in recently recovered subjects with AN as well as subjects with bulimia nervosa [McAdams and Krawczyk, 2013, 2014]. Similarly, the same authors utilized a social attribution task to probe cortical regions related to general social behavior, finding reduced activation in the right inferior frontal gyrus, the bilateral temporoparietal junctions and the bilateral fusiform gyri in a group of recently weight-recovered AN subjects [McAdams and Krawczyk, 2011]. The right angular gyrus differences in activation during benevolence observed here among both the AN-WR and AN-C groups, are consistent with regions previously identified as hypoactive in that earlier study. In sum, these data suggest that anorexia nervosa, as well as the history of anorexia nervosa, may lead to reduced activations of the precuneus and the angular gyri and temporoparietal junction regions during social tasks. Interestingly, the neural differences during the social tasks were most pronounced for positive social interactions in both the AN-C and AN-WR groups but behavioral differences related to benevolence were not observed. This suggests that the trait of developing anorexia nervosa may be more related to neural circuitry differences in encoding and processing positive social interactions than in observable behaviors. Thus, people with AN behave appropriately during positive scenarios but the internal neurocircuitry engaged during those positive social exchanges differs.

Positive Personalizing Bias

In clinical populations, differences in the PPB, a self-report measure from the IPSAQ, have not been reported [Diez-Alegria et al., 2006; Kinderman and Bentall, 1997; Langdon et al., 2013; Wittorf et al., 2012]. However, among eating disorder patients as well as depressed patients, a bias towards an internal attribution for negative events has been reported [Dalgleish et al., 2003; Goebel et al., 1989; Mansfield and Wade, 2000; Morrison et al., 2006]. Consistent with those studies, we did not find differences in the PPB in either patient group or the healthy comparison subjects, but did observe a more negative EB in the AN-C subjects relative to the other two groups.

The relationship between the PPB and neural activity in a large network of regions during benevolence suggests that one's cognitive attribution biases about others impact neural processes that occur during social interaction. These regions overlap considerably with the default mode network (DMN). The DMN includes a number of regions

related to social processing, including self-other distinctions and theory-of-mind [Li et al., 2014]. During a benevolent interaction here, the player's partner has now given proportionately more money than our subject. Ideally, one would recognize generosity, and reason about why the other person has become kinder. A high PPB, or an overall belief that "people are good so good things happen to me" appears to reduce the engagement of neural regions following the experience of generosity in the game. In healthy subjects, impairments in theory of mind have been associated with elevated positive and negative personalizing biases [Kinderman et al., 1998], supporting an idea that one's personalizing bias may relate to self-relevant social reasoning. As the AN-C, AN-WR, and HC groups in this study all showed a similar relationship between the PPB and these neural activations, personalizing biases might provide a specific cognitive target that is helpful in assessment of social brain function.

Cabanis et al. [2013] recently examined the neural basis for self and other attributions in healthy controls, modeled after situations utilized in the IPSAQ. Subjects were asked to attribute situations to themselves or another person, and half of the situations were positive and half negative. First, self-attributions activated the posterior precuneus, with positive self-attributions engaging a more anterior region of the precuneus. The right posterior cingulate was also associated with positive statements, irrespective of self or other attribution. This relationship of the precuneus and posterior cingulate with positive attributions is consistent with our findings that these regions were engaged more during rounds with benevolence. Second, self-attributed negative statements activated the bilateral insula. The insula, another region in the DMN, has been frequently targeted as showing altered neural function in AN using both taste and body image stimuli (for review, see [Nunn et al., 2011]). In the context of this work, we observed right insula activation during benevolence for all three subject groups but found clusters in the bilateral insula during malevolence only for the HC and AN-WR groups (Fig. 2A, Supporting Information Fig. S1, Tables S2 and S3), and did not find any group differences in insula activation. Previously using the trust game, King-Casas et al. [2008] reported that healthy people suppressed insula activity during generous offers in contrast to the subjects with borderline personality disorder who did not alter insula activity for generous offers. In sum, the insula may play an important role for evaluating negative components of social self-evaluation, whereas the precuneus and posterior cingulate may be engaged for the evaluation of positive social interactions. Dysfunctions of the DMN may contribute to anorexia nervosa, and regional differences within the DMN may relate to processing the valences of social and self behaviors.

Limitations

There are limitations to this study. First, the extent that playing the trust game in an MRI scanner corresponds to real-world, social interactive behavior cannot be firmly established. However, behavioral and neural responses obtained from game-play using the same computer-simulated investor agent are indistinguishable from data collected while playing an actual healthy human investor [King-Casas et al., 2008], supporting the utility of this game as a simulator of typical human interactions. Another limitation is that the PPB has not been extensively examined in either healthy or clinical populations. Studies that can connect this cognitive bias to clinical illness, treatments, and outcomes are needed. Finally, although we utilized clear and objective criteria to assign each patient-subject to a clinical group, there are no clinically-standard criteria for recovery in anorexia nervosa. Some patients in the currently-ill group might be termed early-recovery because of recent weight gain, whereas others were chronically-ill. Some of the patients in the weight-recovered group continued to report eating disorder symptoms. However, both of these issues would reduce detection of neural or behavioral differences across the clinical groups. Nevertheless, it is possible that even more fully-recovered patients with anorexia nervosa might show fewer differences in comparison to healthy subjects. Use of medication is an additional factor might benefit from further consideration. However, a recent meta-analysis of antidepressant effects on neural activations reported that antidepressant use increases neural responses to positive stimuli [Ma, 2015]. Again, our data are in the opposite direction (less response to positive stimuli in the medication-use groups) as would be anticipated based on that report. Nevertheless, differences in prior exposure to antidepressant medications might lead to long-term changes related to responsivity to positive stimuli. Finally, other clinical factors, such as history of trauma, comorbid diagnoses, or history of prior illicit drug use, might be relevant but limitations of sample size and the measured and actual characteristics of the sample precluded their consideration. In sum, additional work will be important to clarify which neural differences are related to state of having anorexia nervosa, the trait of being susceptible to developing anorexia nervosa, or other environmental factors such as having been exposed to antidepressants or other treatments for anorexia nervosa.

CONCLUSION

Our results suggest that neural differences in the evaluation of positive social interactions may be a predisposing trait that contributes to the development of anorexia nervosa whereas neural changes related to understanding other people's negative behaviors may be important for weight-recovery following anorexia nervosa. Murray et al. [2015] recently applied task-dependent meta-analytic connectivity modeling with resting state connectivity to identify neural networks related to self-processing and other-processing, including only studies of healthy human subjects. They

reported that the posterior cingulate, precuneus, and temporoparietal junctions compose an other-processing network, whereas the anterior cingulate and insula are specific for self-processing. In this work, we identified altered activations throughout the other-processing network, particularly during benevolent interactions in anorexia nervosa. Furthermore, we identify an office-based metric strongly related to the engagement of many regions in the DMN network, as well as in the other-processing network, during benevolence. From a clinical perspective, the PPB might both provide an assessment related to other-brain function and serve as a potential target for directed, cognitive interventions. This difficulty in recognizing and responding to kindness may be relevant to other psychiatric illnesses such as borderline personality disorder, depression, or anxiety, and patients with this problem may derive benefits from treatments focusing on understanding positive and negative social interactions. Interestingly, in reviewing the regional differences associated with benevolence and the PPB, both the AN-WR and AN-C showed diminished neural activity in the bilateral TPJ but the AN-WR group had similar activity as the HC group in the PC and the dACC clusters (Fig. 3B). Typically, cortical processing regions further from sensory processing are considered the most amenable to neuroplasticity and learning effects. This supports a theory that a biological trait related to diminished neural responses in the perception of kindness may contribute to the development of anorexia nervosa but can be partially overcome with treatment. Ideally, neuroimaging studies and attributional bias measures before and after treatment in concert with long-term clinical outcome measures may lead to a mechanistic understanding of how treatments for anorexia nervosa compensate for biological trait differences.

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