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Trustworthiness appraisal deficits in borderline personality disorder are associated with prefrontal cortex, not amygdala, impairment

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ABSTRACT

Background: Borderline Personality Disorder (BPD) is associated with sensitivity to signals of interpersonal threats and misplaced trust in others. The amygdala, an integral part of the threat evaluation and response network, responds to both fear- and trust-related stimuli in non-clinical samples, and is more sensitive to emotional stimuli in BPD compared to controls. However, it is unknown whether the amygdalar response can account for deficits of trust and elevated sensitivity to interpersonal threat in BPD.

Methods: Facial stimuli were presented to 16 medication-free women with BPD and 17 demographically-matched healthy controls (total n = 33). Participants appraised fearfulness or trustworthiness of the stimuli while BOLD fMRI was obtained.

Results: Though BPD participants judged stimuli as less trustworthy compared to controls, trustworthiness did not correlate with amygdalar activity in either group. Trustworthiness correlated with prefrontal regional activity in the insula and lateral prefrontal cortex. Prefrontal BOLD activity while appraising trustworthiness was smaller in BPD compared to controls, and the size of the reduction was proportional to each participant's response bias.

Conclusions: Neural substrates of trustworthiness appraisal are associated with the lateral prefrontal cortex and insula, not amygdala, suggesting that untrustworthy stimuli do not elicit a subcortical threat response. Current models of BPD and its treatment may need to include a focus on improving impairments in frontally mediated trustworthiness appraisal in addition to amygdala- driven emotional hyper-reactivity.

1. Introduction

Heightened sensitivity to threat signals in interpersonal relationships and a misplaced trust in others are common vulnerabilities in Borderline Personality Disorder (BPD) (Gunderson and Lyons-Ruth, 2008; Arntz et al., 2000; Arntz et al., 2009). Individuals with BPD are prone to judge others as more hostile (Barnow et al., 2009), are more likely to detect anger in ambiguous faces (Domes et al., 2008), to recognize angry faces faster than healthy controls (Bertsch et al., 2013), and to exhibit an elevated affective startle reflex (Hazlett et al., 2007). BPD is also associated with greater mistrust of others, characterized by a response bias during trustworthiness appraisal (Fertuck et al., 2013; Miano et al., 2013). Furthermore, the emotional valence of a neutral face, i.e., the degree to which the face appears to be happy or angry, influences the visual assessment of trustworthiness in non-clinical individuals and has led to the hypothesis that appraisal of trustworthiness is actually an assessment of interpersonal threat (Oosterhof and Todorov, 2008). Thus, greater sensitivity to cues of interpersonal threat in BPD (Fertuck et al., 2009; Dinsdale and Crespi, 2013; Frick et al., 2012) may explain its association with elevated mistrust of others (Fertuck et al., 2013).

The neural mechanisms of threat appraisal have been studied extensively, and, it is widely accepted that the amygdala is an integral

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part of the threat appraisal and response system (Costafreda et al., 2008; Sergerie et al., 2008; Adolphs, 2013). The amygdala has also been proposed to be an important structure in the appraisal of trustworthiness (Adolphs et al., 1998; Engell et al., 2007; Said et al., 2008; Winston et al., 2002). Bilateral lesions of the amygdala result in appraisals of elevated trustworthiness and approachability in both monkeys (Amaral, 2002) and humans (Adolphs et al., 1998). Faces judged to be untrustworthy are associated with greater amygdala activity than trustworthy faces (Engell et al., 2007; Said et al., 2008; Winston et al., 2002). Furthermore, after interpersonal betrayal, nasally administered oxytocin reduces amygdala activity, and preserves trust and cooperation (Baumgartner et al., 2008). These findings suggest that, in non-clinical adults, appraisal of trustworthiness involves the amygdala, and cues of interpersonal threat, such as expressions of anger or aggression, lead to an amygdala-based threat signal. By extension, greater mistrust of others in BPD may plausibly be a consequence of amygdala hyperactivity (Fertuck et al., 2013). In fact, several studies have reported that individuals with BPD exhibit greater amygdala activation to a wide range of interpersonal and emotional stimuli compared to controls (Donegan et al., 2003; Herpertz, 2003; Koenigsberg et al., 2009; Minzenberg et al., 2007), though hypoactivation has also been reported (Dudas et al., 2017). However, though BPD has been associated with elevated amygdala activity to emotional stimuli and reduced interpersonal trust, a direct link between the elevated amygdala activity and impairment in trustworthiness appraisal has not been established. In the present study, facial expressions were systematically varied along the fearfulness or trustworthiness dimensions, and appraised by a BPD and a healthy control group. We tested the hypothesis that the response bias toward judging faces as untrustworthy, characteristic of BPD, will be correlated with amygdala hyperactivity. We also performed whole-brain analyses to determine whether other regions were related to trustworthiness appraisal deficits in BPD.

2. Methods and materials

2.1. Participant characteristics

All participants were female between the ages of 18 and 45 years; 17 were healthy controls and 16 had a DSM-IV diagnosis of BPD (APA, 2000). Participants were recruited via advertisements and referral through a large, metropolitan hospital as part of ongoing clinical studies in mood disorders, suicidal behavior, and BPD. None of those with BPD were taking psychotropic medications while participating in the study, though 60% had a history of use of psychiatric medication. Exclusion criteria for the BPD group included a current major depressive episode, psychotic disorder, current substance use disorder, or a recent suicide attempt (in the last 6 months). The healthy control group was matched on demographics (age, ethnic/racial frequency, marital status), education level, and verbal IQ (the vocabulary subtest of the Wechsler Adult Intelligence Scale)(Wechsler, 1997), and was assessed with semi-structured interview to rule out a history of psychiatric or substance use disorder. Institutional Review Boards at two institutions approved the study. Fifty-eight participants signed consent, and 43 completed all assessments and the fMRI scan. Table 1 summarizes the demographic and clinical descriptions, and Supplementary Table 1 summarizes the clinical diagnoses of the BPD sample. Notably, 37.5% of the BPD group reported past of substance abuse or dependence, 68.8% had a past major depressive disorder, and none had a current or past bipolar or PTSD diagnosis.

2.2. Clinical assessment

For individuals with BPD and controls, diagnoses were determined by Structured Clinical Interview for DSM-IV, Patient Edition (SCID-I) (Spitzer et al., 1990) and the Structured Clinical Interview for DSM-IV

Table 1
Demographic and Clinical Characteristics.

	BPD (n = 16)		Controls (n = 17)			
	M	*SD*	*M*	*SD*	*t*	*p*
Demographic Characteristics						
Age	25.94	5.47	23.71	3.35	1.42	*n.s.*
Education (years)	15.31	1.89	15.82	1.78	-0.80	*n.s.*
WAIS (Vocabulary Subtest Scaled Score)	13.94	1.95	14.12	2.47	-0.23	*n.s.*
	N	***%***	***N***	***%***	χ^2	***p***
Race/Ethnicity						
Asian	3	18.8	5	29.4		
Black or African American	2	12.5	1	5.9		
White	7	43.8	11	64.7		
More than one race	4	25.0	0	0.0		
Hispanic/Latino	5	31.3	4	23.5		
White	7	43.8	11	64.7	1.46	n.s.
Non-White	9	56.3	6	35.3		
Married	2	12.5	0	0.0	2.26	n.s.
Not married	14	87.5	17	100.0		
Clinical Characteristics						
Rating scales scores	***M***	***SD***	***M***	***SD***	***t***	***p***
Hamilton Depression Inventory	10.25	5.80	0.82	1.67	6.45	*0.000*
Buss-Durkee	32.25	9.60	13.29	7.63	6.31	*0.000*
POMS	39.63	31.79	2.47	12.80	4.46	*0.000*
Rejection Sensitivity Questionnaire	15.56	6.96	5.86	2.92	5.27	*0.000*
GAS score	62.13	8.35	87.12	6.46	-9.65	*0.000*
	N	**%**	**N**	**%**		
Past suicide attempter	8	50.0	0	0.0		
Physical or sexual abuse (prior to age 18)	7	43.8	0	0.0		
Sexual Abuse	5	31.3	0	0.0		
Physical abuse	5	31.3	0	0.0		
Lifetime non-suicidal self-injury (NSSI)	10	62.5	0	0.0		

+ = $p < 0.10$, *$p < 0.05$, **$p < 0.01$, *n.s.* = not significant; all two-tailed tests

Axis II Personality Disorders (SCID-II) (First et al., 1997). Reliability studies within our research division yielded the following intra-class correlation coefficients (ICCs) (criterion levels 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). Depression severity was assessed using the Hamilton Depression Rating Scale (Ham-D; (Hamilton, 1960)). Concurrent negative emotional state was assessed with the Profile of Mood States (McNair et al., 1981) a 65-item self-report questionnaire that provides a total score of state negative emotion scores based on 6 transient emotional states: tension-anxiety, depression-dejection, anger-hostility, confusion-bewilderment, vigor-activity, and fatigue. Hostility and aggression were assessed using the Buss Durkee Hostility Inventory (BDHI; (Buss and Durkee, 1957)). Abuse history was assessed as part of the demographic interview, which asks participants whether they have experienced physical and sexual abuse before age 18. We assessed the number of prior suicide attempts from the Columbia Suicide History interview (Posner et al., 2011). The Rejection Sensitivity Questionnaire was used to assess anxious anticipation and expectation of interpersonal rejection (Downey and Feldman, 1996) (See Table 1 for clinical characteristics).

2.3. Trustworthiness-fear face appraisal task

We utilized a task developed and validated by our group (Fertuck et al., 2013; Fertuck et al., 2016) to measure an individual's capacity to make subtle discriminations between facial features that indicate potential interpersonal threats, expressions of fear and of trustworthiness. Trustworthy faces were male, computer generated avatars selected from the stimuli developed and psychometrically validated by Todorov and colleagues (Todorov et al., 2008). Facial fear stimuli were selected from the NimStim Face database (Tottenham et al., 2009) and identical to those used in Fertuck et al. (Fertuck et al., 2013).

Faces at opposite extremes (neutral vs. fearful) or (trustworthy vs. untrustworthy) were morphed together in steps of 10% to create intermediate fear and trust values (Morpher software for Windows, version 3.1, M. Fujimiya). Individuals were presented with faces that varied along the fear or trustworthiness dimensions and asked to judge each face on a five-point Likert scale (where 1 is neutral or trustworthy and 5 is fearful or untrustworthy). (See (Fertuck et al., 2013) for more details on the development of the task and Supplementary Fig. 1 and Supplementary Methods for sample stimuli and further elaboration of the procedure).

Subjective appraisal parameters were determined by fitting the behavioral data (i.e. rating versus % morph) to a logistic function of the form, ($y = \alpha + \beta/(1 + e^{-\lambda(x+50)})$) where x is the morph percentage of the stimulus, y is the mean subjective rating, and the free parameters are α (the offset or bias), β (the scaling or sensitivity), and λ (the slope or discriminability) of the psychometric function. Each participant's responses were checked to confirm that they completed the tasks as instructed (i.e. that subjective responses were not random but showed a monotonically increasing relationship with morph value). From those participants who completed the fMRI task, 2 BPD participants were excluded due to corruption of the data, and 4 BPD and 4 control participants were excluded because their ratings of either the trust or fear stimuli indicated a lack of discrimination between the most and least untrustworthy or fearful stimuli. All results, then, were based on data from 16 BPD patients and 17 healthy controls.

2.4. Functional imaging

2.4.1. fMRI parameters

Functional MRI was performed on a 1.5 Tesla GE Signa scanner using the EPI-BOLD sequence (TR = 2.0, TE = 86, flip angle = 34, number of slices = 27, array size = 64 × 64, voxel size = 3.1 mm × 3.1 mm × 4.0 mm, number of volumes = 150, duration of run = 6 min. Structural scans were performed using the 3D SPGR sequence (124 slices, 256 × 256, FOV = 200 mm).

2.4.2. fMRI data analysis

All analysis was done using the FMRIB Software Library (FSL 5.0.10; (Jenkinson et al., 2012) and Matlab 2017a. Preprocessing consisted of motion correction (McFlirt), slice timing correction, high-pass filtering (> 50 s), and spatial filtering (FWHM = 5 mm). Relative head motion of 0.5 mm was set as a threshold and runs exceeding this value were excluded (none reached the threshold). Motion parameters (3 translations, 3 rotations, derivative and quadratic terms; 18 regressors total), CSF and white matter activity were included as confound regressors. Standard statistical parametric mapping techniques (FEAT) were performed in original T2* space. Group analyses were performed using FEAT in MNI152 space at 2 mm isotropic resolution. Voxel-wise activation thresholds were set at p = 0.05, correction for multiple comparisons was done using Gaussian Random Field Theory with a cluster threshold of p = 0.001. A whole brain mask was used to exclude voxels outside the brain.

For each functional run, a regression model was created assuming three neural processes: (1) an unmodulated process, (2) the subjective appraisal of the stimulus, and (3) the quadratic term of the appraisal. The unmodulated regressor consisted of a set of boxcars in which each boxcar began at stimulus onset and ended when the subject made a response. The height of each boxcar was equal to 1 and represented any task-general activity (e.g. working memory, spatial attention, sensory processing, and other processes) that do not differ between conditions). The appraisal regressor had an identical temporal structure to the unmodulated regressor but the height of each boxcar was proportional to the participant's subjective mean rating of the stimulus for the trust or fear decision. The quadratic regressor used an identical temporal structure to the appraisal regressor but with amplitude generated by demeaning the subject's ratings and taking the absolute value. Trials with response times > 2.5 standard deviations outside the mean were excluded from the behavioral and imaging analyses. Each regressor was convolved with a custom HRF, which was individually estimated for each participant from their primary visual activity (Grinband et al., 2008); custom HRFs have been shown to reduce both model error (Handwerker et al., 2004) and bias (Grinband et al., 2017) relative to the canonical HRF. A fixed effects (2nd level, within subject) and a mixed-effects (3rd level, between subjects) analysis was done to compare patients with controls for the trust and fear appraisal regressors. We performed two ROI analyses of the amygdala. First, we created a mask by searching the Neurosynth database (Yarkoni et al., 2011) using the keyword “threat”. The reverse inference map was thresholded at 7 and binarized resulting in a bilateral amygdala mask positioned primarily over the lateral nuclei of the amygdala (MNI: −22, −2, −20; 24, −4, −20). A second analysis was performed subject-specific masks of threat-sensitive voxels. These voxels were identified as voxels modulated by subjective appraisal of fearfulness, thresholded at > 1.6) and intersected with a whole amygdala mask. Both the Neurosynth mask and the subject-specific mask were used to average the parameter estimates of the masked voxels during trustworthiness appraisal. The Kolmogorov-Smirinov Test was used test for deviations from Normality for all *t*-tests (Supplementary Results). Cohen's D (*d*) was computed as the group mean divided by sample standard deviation.

2.4.3. Assumptions

Our goal was to determine whether subjective appraisal of trustworthiness depends on threat signals generated by the amygdala. We assumed that fearfulness appraisal elicits threat signals in the amygdala and that any activity in the amygdala that increased with untrustworthiness would also represent a threat signal. Given these assumptions, if our paradigm could generate threat signals in the amygdala using fearful stimuli, it should also be able to generate amygdala threat signals using untrustworthy stimuli. Furthermore, since BPD is associated with elevated sensitivity to social threat and a bias toward judging others as untrustworthy, BPD subjects should show elevated threat activity in the amygdala compared to controls using untrustworthy stimuli.

3. Results

Consistent with our previous study (Fertuck et al., 2013), the BPD group showed a response bias to judge faces as untrustworthy (*t*-test of bias: control, M = 1.6, SD = 0.15; BPD, M = 2.1, SD = 0.16, t(28) = 2.44, z = 3.23, p = 0.02) and had a smaller dynamic range, or, sensitivity (t-test for scale: control, M = 3.08, SD = 0.41; BPD, M = 1.71, SD = 0.23, t(28) = 2.8, z = 3.98, p < 0.01). Trustworthiness appraisal did not result in significant group differences in discriminability (Fig. 1). Appraisal of fearfulness did not show any significant group differences for bias (p = 0.47), sensitivity (p = 0.14), or discriminability (p = 0.49). An analysis of variance showed that the BPD group exhibited longer RTs than controls (Fig. 1) for trustworthiness (rating, p = 0.002; group, p < 0.0001) and fearfulness (rating, $p < 1 \times 10^{-6}$; group, p = 0.007), and no significant interactions.

To identify the neural structures associated with the two types of appraisals, we performed a whole brain analysis, regressing the appraisal ratings made by each subject on the BOLD data. Consistent with most fMRI studies of fear processing (Rauch et al., 2000; Whalen et al., 1998), both amygdalae were robustly modulated by subjective appraisals of the fearful stimuli – BOLD magnitude increased as a function of the subjective rating of intensity of the stimulus (Fig. 2A; peak response, MNI: 24, −8, −14, Z = 3.83; −24, −4, −14, Z = 3.56; Supplementary Table 2). If the threat-related cues detected by the amygdala are also important for trustworthiness appraisal, then amygdala activity should be modulated by trustworthiness. However, the whole brain analysis showed no activity in the amygdala that was significantly modulated by stimulus trustworthiness (Fig. 2B; Supplementary Table 2).

Averaging across voxels can improve the signal to noise ratio; thus, we performed an ROI analysis of the amygdala using a mask generated on Neurosynth using the keyword “threat”. In healthy controls, the mean activity of voxels within the mask showed robust amygdala modulation by subjective fear ratings (p = 0.01, d = 0.70) but contrary to previous work (Engell et al., 2007; Winston et al., 2002), no significant modulation by subjective trust ratings (p = 0.33, d = 0.25). In

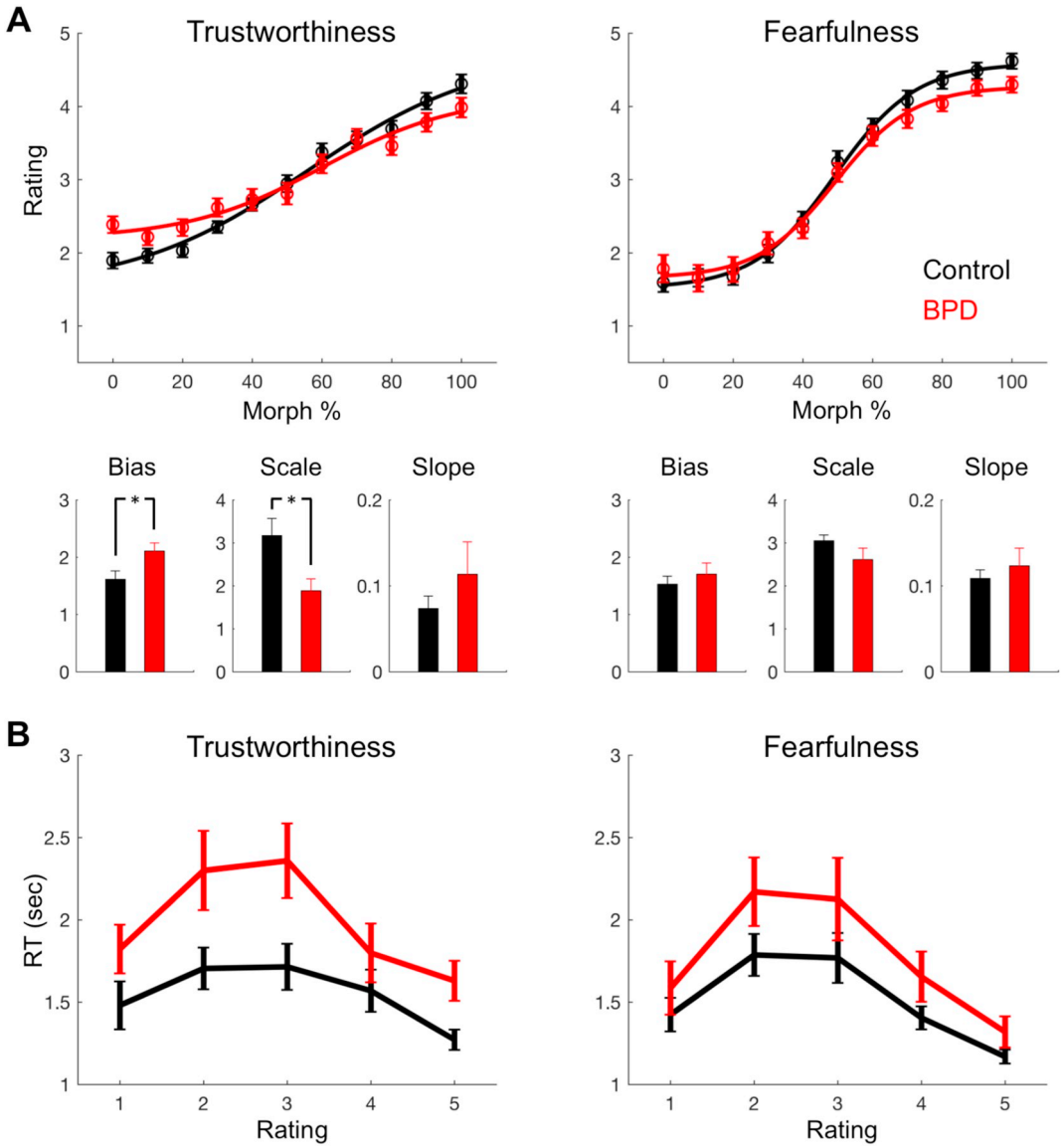

Fig. 1. Appraisal of trustworthiness and fearfulness. (A) For both tasks, participants demonstrated categorical judgments (i.e. a sigmoidal, monotonically increasing relationship). Behavioral responses were fit with logistic functions using three parameters: offset, scale, and slope. A comparison of the three parameters showed that, consistent with our previous work, the offset parameter in the trustworthiness task was significantly higher in the BPD group, indicating a bias toward judging others as “untrustworthy.” In addition, the scale parameter was smaller for BPD than controls, indicating a reduced dynamic range of responses. Remaining parameters for the two tasks were not significantly different. (B) Response times were greater for patients than controls on both tasks (ANOVA).

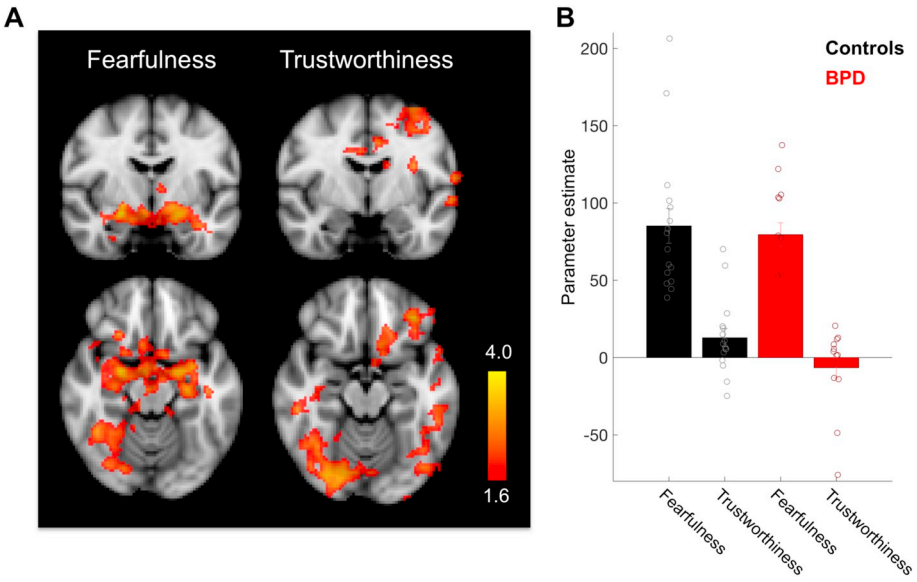

Fig. 2. Monotonically increasing activity. (A) Robust, bilateral activation of the amygdala increased with fearfulness of the stimulus across all participants. A similar, monotonically increasing relationship with untrustworthiness was not present. (B) For each subject, a mask was created representing voxels sensitive to fearfulness within the amygdala and the mean of the parameter estimates was computed. No significant relationship for trustworthiness was present for control or BPD participants, suggesting that untrustworthy stimuli do not produce an amygdala-based fear response. Finally, during trustworthiness appraisal, amygdala activity in BPD participants showed a small, but significant, reduction of response, contrary to the amygdala hyperactivity found in previous BPD studies.

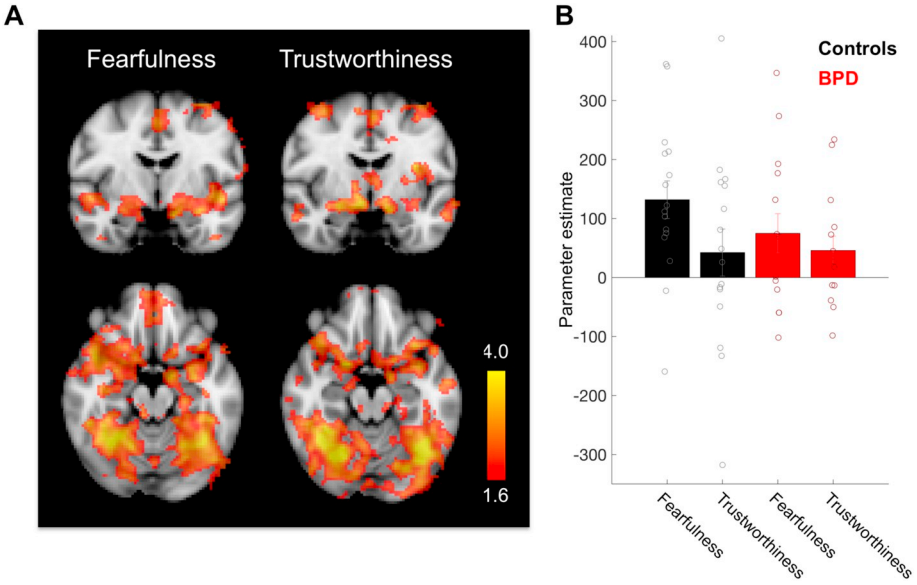

Fig. 3. Quadratically modulated activity. (A) A weak, but significant, quadratic relationship with fearfulness was present in the amygdala. Some voxels with a quadratic relationship to trustworthiness were detected on the striatum-amygdala and csf-amygdala boundaries, though the peak responses of these clusters were outside the amygdala. (B) Using an amygdala mask, the mean response was quadratically related to fearfulness, but not trustworthiness.

the BPD group, no significant activity was detected either by fear ($p = 0.33$, $d = 0.25$) or trust ($p = 0.56$, $d = -0.15$) ratings. Since BPD is associated with elevated sensitivity to interpersonal threats (Barnow et al., 2009; Gunderson and Lyons-Ruth, 2008), if the amygdala were sensitive to untrustworthiness, then BPD subjects should show greater amygdala activation than controls as the stimuli become less trustworthy. However, a comparison of the two groups showed no significant difference between groups for trust ($p = 0.26$, $d = 0.40$) or fear ($p = 0.33$, $d = 0.35$). Fig. 3.

Previous studies have suggested that the effect of trustworthiness appraisal on amygdala activity in healthy controls is best described by a quadratic relationship (Said et al., 2008), (Baas et al., 2008; Said et al., 2009). Though our controls showed a significant quadratic relationship for fear ($p = 0.04$, $d = 0.53$), no significant quadratic relationship for trust ($p = 0.80$, $d = 0.06$) was found. In the BPD group, the quadratic model was not significant for fear ($p = 0.68$, $d = 0.18$), but was significant for trust ($p = 0.02$, $d = 0.65$).

To determine whether the two tasks activate similar brain networks, we compared whole-brain activations (Fig. 4A). Fearfulness appraisal activated primarily sub-cortical regions, whereas trustworthiness appraisal was associated primarily with cortical activity. To dissociate activity specific to fearfulness and trustworthiness appraisal from general decision-making activity related to stimulus intensity, we performed a contrast between task conditions (contrasting fearfulness > trustworthiness and trustworthiness > fearfulness on the appraisal regressor; Fig. 4B). Using a cluster threshold of $p = 0.001$, fearfulness > trustworthiness did not result in significant activations. However, because the amygdala nuclei are small structures, $p = 0.001$ may result in elevated Type II error in subcortical structures. At a cluster threshold of $p = 0.05$, fearfulness-specific activity was localized to subcortical regions, i.e., amygdala and ventral striatum (peak response, MNI: 22, −6, −8), consistent with the previous ROI analysis (i.e. Fig. 2). Moreover, even at a more liberal threshold, no fearfulness-specific activity in the cortex was detected. In contrast, trustworthiness-specific activity was present only in cortical regions, broadly distributed across posterior parietal cortex, and dorsolateral and mediolateral prefrontal cortex, and no spatial overlap of amygdala (Supplementary Table 3).

Because BPD is associated with behavioral abnormalities in trustworthiness appraisal, we hypothesized that the trustworthiness-specific network (i.e. trustworthiness > fearfulness) would show activity differences between BPD and control subjects. We, thus, performed

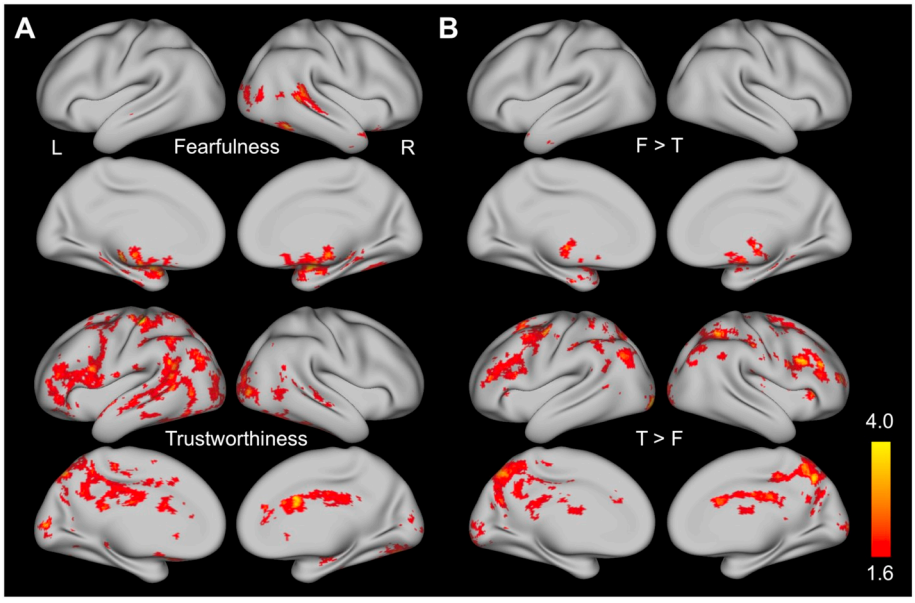

Fig. 4. Whole brain comparison. (A) A whole-brain analysis demonstrates that the monotonic fearfulness response activates primarily subcortical structures i.e. amygdala and ventral striatum, whereas, the trustworthiness response was primarily cortical. (B) To identify activity unique to fearfulness and trustworthiness, and not to general decision processes common to both tasks, fearfulness > trustworthiness and trustworthiness > fearfulness contrasts were performed. Fearfulness-specific activity was localized to amygdala, ventral striatum, and left frontal pole. There was no trustworthiness-specific activity in subcortical structures.

the following contrast: $(\text{trustworthiness} > \text{fearfulness})_{\text{Control}} > (\text{trustworthiness} > \text{fearfulness})_{\text{BPD}}$. BPD participants had lower trustworthiness-specific activity in prefrontal cortex (Fig. 5A), especially anterior insula and lateral PFC (Supplementary Table 3). Finally, to determine whether these group differences were related to individual subjects' decision variables, we intersected voxels that showed activity specific for trustworthiness appraisal (Fig. 4B, trustworthiness > fearfulness) with voxels that differed between groups (5A, $(\text{trustworthiness} > \text{fearfulness})_{\text{Control}} > (\text{trustworthiness} > \text{fearfulness})_{\text{BPD}}$) and compared them to individual differences in response bias and sensitivity. The anterior insula and lateral PFC (Fig. 5B) activity was related to the degree of bias ($r = 0.457$, $p = 0.007$) and sensitivity ($r = 0.597$, $p = 0.0005$) impairment in trustworthiness appraisal (Fig. 5C), such that, the weaker the network activity, the greater the bias toward untrustworthy ratings and the smaller the range of responses.

4. Discussion

The amygdala is an integral part of the threat detection system in humans (Costafreda et al., 2008; Sergerie et al., 2008; Adolphs, 2013), and to the extent that untrustworthy faces represent interpersonal threats, investigators have argued that the amygdala is integral to the appraisal of trustworthiness in non-clinical adults (Engell et al., 2007; Said et al., 2008; Winston et al., 2002). Furthermore, individuals with BPD have been shown to have response biases toward mistrusting others (Fertuck et al., 2013; Miano et al., 2013; Miano et al., 2016) and hyperactive responses of the amygdala to emotional stimuli (Donegan

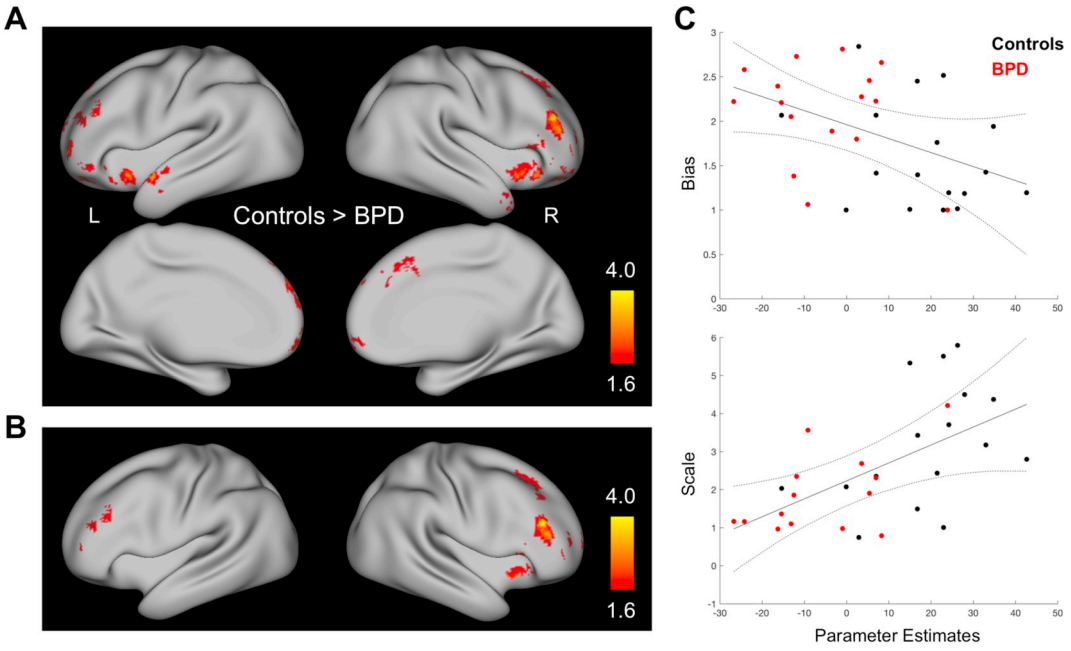

Fig. 5. BPD-related deficits. (A) BPD participants showed reduced trust-specific activity in the anterior insula and lateral prefrontal cortex. (B) The intersection of voxels that were sensitive to trustworthiness and significantly reduced in BPD localized to anterior insula and lateral prefrontal cortex. (C) These intersecting voxels were negatively related to bias (i.e. the greater the bias toward mistrusting others, the larger the reduction in activation) and positively correlated to scale (i.e. the smaller the dynamic range of responses, the larger the reduction in activation). Dashed lines represent 95% confidence interval.

et al., 2003; Herpertz, 2003; Koenigsberg et al., 2009; Minzenberg et al., 2007). Our goal was to test whether amygdala hyperactivity could explain the response biases in BPD during the appraisal of trustworthiness (Fertuck et al., 2013; Miano et al., 2013; Miano et al., 2016). Surprisingly, we found no relationship between trustworthiness appraisal and amygdala activity, and no difference in amygdala activity between BPD and control participants. Instead, trustworthiness appraisal deficits in BPD were associated with blunted prefrontal activity in anterior insula and lateral PFC compared to controls.

Evidence that trustworthiness activates the amygdala has been inconsistent. Studies that categorically compared trustworthy versus untrustworthy stimuli typically find greater amygdala responses to untrustworthy faces (Blasi et al., 2009; Pinkham et al., 2008a; Pinkham et al., 2008b; van Rijn et al., 2012). Similarly, some parametric studies have demonstrated that amygdala activity increases monotonically with untrustworthiness (Engell et al., 2007; Winston et al., 2002). However, others found a quadratic, not monotonic, relationship, between trustworthiness and amygdala responses (Baas et al., 2008; Said et al., 2009). Contrary to these previous studies, we found no evidence that amygdala activity increases monotonically or quadratically with untrustworthiness in healthy controls. This lack of response was not due to sensitivity of our behavioral paradigm. In fact, consistent with our previous studies (Fertuck et al., 2013; Miano et al., 2013; Miano et al., 2016), our behavioral data showed a sigmoidal relationship between stimulus and response, and a response bias in BPD for judging stimuli as less trustworthy, but not more fearful. Moreover, the trustworthiness-stimuli were psychometrically discriminable by both groups with a dynamic range similar to the fearful stimuli and the fearful stimuli elicited robust, bilateral amygdala responses that scaled parametrically with subjective intensity. This suggests that if trustworthiness decisions depended on threat-related amygdala activity, modulation of amygdala by trustworthiness would have been detectable with our paradigm.

Previous parametric studies focused mostly on “implicit,” or subconscious, processing of trustworthiness, distracting subjects from the trustworthiness dimension with an irrelevant task (Engell et al., 2007; Winston et al., 2002; Baas et al., 2008) or using very short (200 ms) stimulus durations (Said et al., 2009). While implicit trustworthiness processing is commonly referred to as “trustworthiness decisions,” it is not clear that any amygdala activity that is correlated with trustworthiness, but also lacks an associated behavioral response, actually represents a decision process. Instead, this activity is more likely to be related to low-level, perceptual processing (Whalen et al., 1998; Anderson et al., 2003; Garvert et al., 2014; Jiang et al., 2009; Morris et al., 1998; Santos et al., 2011; Etkin et al., 2004). In fact, trustworthiness has been shown to be decomposable into two perceptual factors – dominance and emotional valence, where emotional valence is expressed as facial features ranging from happy to angry (Oosterhof and Todorov, 2008; Sutherland et al., 2013). However, while anger has been shown to represent a cue for untrustworthiness, a meta-analysis of 105 imaging studies has not found it to reliably activate the amygdala (Fusar-Poli et al., 2009). Moreover, because the amygdala generally responds to emotional faces (Fusar-Poli et al., 2009), even at subthreshold levels (Whalen et al., 1998; Anderson et al., 2003; Garvert et al., 2014; Jiang et al., 2009; Morris et al., 1998; Santos et al., 2011; Etkin et al., 2004), the implicit or rapid processing of trustworthiness by the amygdala may actually reflect the emotional valence detectable in the stimulus rather than the appraisal of trustworthiness per se.

Facial cues associated with low trustworthiness are not necessarily reliable or immediate expressions of threat, compared to reliable cues such as an image of a snake or a pointed gun. Rather, trustworthiness appraisal may be better conceptualized as a probabilistic prediction about the likelihood of interpersonal betrayal or exploitation by others. Probabilistic reasoning, especially in social contexts, has been associated with prefrontal cortical processing (Barbey et al., 2009; Domenech and Koechlin, 2015; Chambon et al., 2017). Our results show that trustworthiness is mediated by prefrontal cortical (posterior parietal cortex, anterior insula, and lateral PFC) activity and that trustworthiness appraisal deficits in BPD are also mediated by the same regions.

The trustworthiness appraisal impairments identified here may help elucidate mechanisms of turbulent relationships in BPD. Individuals with BPD maintain unstable interpersonal ties, as they oscillate between establishing new relationships and ending them (Clifton et al., 2007). Some of the most high risk diagnostic criteria of BPD such as self-injury, suicidality, intense and inappropriate anger, impulsivity, and heightened emotional sensitivity are mediated by the quality of interpersonal bonds between the person with BPD and significant others (Brodsky et al., 2006). Facial expressions within in interpersonal contexts are salient stimuli, and can anticipate mistrust and the expectation of rejection (Miano et al., 2013; Downey et al., 2004; Ayduk et al., 2008; Roepke et al., 2012). Consequently, the trustworthiness appraisal impairments in BPD can increase their propensity interpersonal conflicts, lead to uncooperative exchanges in social interactions, threaten the formation of new relationships, and undermine long-term relationships. The trustworthiness discriminability impairment mediated by prefrontal cortex processes may help clinicians to understand commonly observed interpersonal dynamics in BPD. For instance, individuals with BPD often reflexively enter into new relations with questionable partners, while simultaneously expressing extreme caution and suspiciousness toward presumably helpful and supportive others.

Improving accurate appraisal of trustworthiness in interpersonal and therapeutic relationships in BPD may be crucial to therapeutic improvement, and dissociating the roles of prefrontal cortex and amygdala in trustworthiness appraisal may aid in sharpening intervention targets. Prominent, evidence-based therapies for BPD such as Transference Focused Psychotherapy (TFP, (Kernberg OF et al., 2008)) and Mentalization-Based Therapy (MBT, (Bateman and Fonagy, 2004)), focus implicitly and explicitly (Fonagy and Allison, 2014) on enhancing trustworthiness appraisal by fostering frontally-mediated social reappraisal processes. However, there may yet be untapped strategies and interventions that those with BPD, such as improving accurate probabilistic reasoning around trustworthiness appraisals.

4.1. Limitations

Without a psychiatric control group, the specificity of the trustworthiness impairment findings has yet to be established. However, we have published work using the same trustworthiness and fear tasks in a PTSD sample compared to a trauma-exposed/no PTSD control group and a healthy control group. The PTSD group showed a response bias toward judging stimuli as more trustworthy compared to the trauma-exposed controls (Fertuck et al., 2016). This is opposite to our BPD findings, which show a bias toward less trustworthy appraisals, and suggests some clinical specificity of our results. Finally, although our BPD sample has relatively few co-morbidities, the mean Global Assessment of Functioning (GAF) score of the group was 55.12, consistent with multi-site, longitudinal studies of BPD (Gunderson et al., 2011) and suggesting that our BPD group had comparable severity of illness.

4.2. Conclusions

In summary, we found no evidence of amygdala hyperactivity in BPD subjects during appraisal of trustworthiness. Our results show, however, that trustworthiness biases in BPD involve higher order prefrontal cortical regions.

Additionally, further study is needed to clarify impact of emotional expressions (e.g., appraisal of anger in facial stimuli may overlap with untrustworthiness perception) on trustworthiness appraisal and amygdala activity in BPD and comparison groups.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2018.101616.

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