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Identifying Disease-Specific Neural Reactivity to Psychosocial Stress in Borderline Personality Disorder

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ABSTRACT

BACKGROUND: Patients with borderline personality disorder (BPD) typically present emotion dysregulation (ED) when faced with adversity. However, it is argued that altered stress response may be more influenced by ED than BPD-specific traits. Here, we investigated this issue with functional magnetic resonance imaging using another ED condition as clinical control, i.e., bipolar disorder (BD), and controlling for ED traits.

METHODS: We recruited 17 patients with BD, 24 patients with BPD, and 32 healthy control (HC) subjects. We adapted a functional magnetic resonance imaging–compatible psychosocial stressor task (Montreal Imaging Stress Task) in which participants are placed under time pressure when performing mental calculations and then receive immediate performance feedback (positive, negative, and neutral). ED traits were measured via self-report questionnaires targeting cognitive emotion dysregulation, affective lability, and trait anger and anxiety.

RESULTS: Relative to patients with BD and HC subjects, patients with BPD exhibited overactive corticolimbic reactivity across all conditions, particularly in self-monitoring and emotion regulation regions such as the orbitofrontal cortex and anterior insula, even when controlling for ED. Conversely, patients with BD exhibited hypoactive corticolimbic reactivity to all feedback conditions compared with patients with BPD and HC subjects, even after controlling for ED. HC subjects exhibited significantly lower amygdala/hippocampus activity compared with both clinical groups, although this did not survive when controlling for ED.

CONCLUSIONS: This study provides new insight into BPD-specific neural stress responding, suggesting hyperactive self- and emotion-regulatory neural psychosocial stress responding, independent of ED traits. The findings also highlight the importance of considering BPD as a diagnostic profile distinguishable from other ED disorder clinical groups.

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Patients diagnosed with borderline personality disorder (BPD) are characterized by pervasive instability of affect, interpersonal relationships, and self-image (1). Emotion dysregulation (ED), a core trait of BPD (2,3), is linked to affective lability and high rejection sensitivity. These traits likely underlie bouts of rage and intense feelings of anger (4), often provoked by interpersonal threat signaling rejection and exclusion (5).

Clinical neuroimaging and physiological studies point to impaired neural psychosocial stress reactivity in BPD. Social stress, e.g., rejection, elicits enhanced responses in the dorsal anterior cingulate cortex (dACC), precuneus, medial prefrontal cortex (PFC), and insula in patients with BPD relative to healthy control (HC) subjects (6). When imagining anger-eliciting scenarios, patients with BPD show increased activation in the insula and striatum compared with HC subjects (7). Finally, negative stimuli elicit hyperactive BPD amygdala reactivity (8). In physiological literature, meta-analytic evidence shows dampened cortisol during psychosocial stress reactivity in patients with BPD in comparison to HC subjects and those with other personality disorders, suggesting syndrome-specific psychosocial stress reactivity (9). Dampened cortisol reactivity to psychosocial stress correlates with increased activity in corticolimbic structures, e.g., medial PFC (10), pointing to an exaggerated BPD corticolimbic responding to social stress.

Still, an ongoing debate exists over whether BPD stress reactivity results from BPD-specific features or generalized traits related to ED (11). In a study showing nonsignificant differences in stress responding with respect to general anxiety disorder, evidence suggests that BPD physiological stress reactivity is more specific to ED traits than unique BPD features (11). Still, conclusions are premature without assessing brain functioning during stress response and comparing other ED disorder groups. In addition, controlling for ED-related affective domains concurrently would be crucial for isolating BPD-specific traits underlying neural stress responding.

This study, therefore, aimed to investigate whole-brain neural reactivity to psychosocial stress in patients with BPD

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relative to HC subjects and patients with bipolar disorder (BD), an ED disorder group. BD constitutes severe ED characterized by pronounced emotional lability (12) and voluntary emotional control deficits (13). ED in BD is attributed to altered functional corticolimbic connectivity (14), reflecting impaired cognitive control during emotion events. Indeed, increased limbic activity, particularly within the amygdala, may reflect heightened emotional reactivity to emotional stimuli (15) and may result from decreased cognitive control over limbic structures (16). This emphasizes the importance of both dorsal frontal and limbic areas in emotion regulation in BD (17). Thus, were BPD stress reactivity to be disorder specific, BD should stand as an important clinical group to demonstrate these effects on neural responding in patients with BPD.

Here, we used a magnetic resonance imaging (MRI)–compatible computerized paradigm inducing psychosocial stress via feedback on personal performance of mental calculations in patients with BD, patients with BPD, and HC subjects (18). Psychosocial stress tasks are instrumental in assessing neurobiological reactivity to interpersonal stress (9). To further control for the influence of ED traits in BPD stress responding, we assessed various self-reported traits related to ED, i.e., affective lability, anger, anxiety, and cognitive ED (cED). We predict that compared with patients with BD and HC subjects, patients with BPD exhibit global corticolimbic hyperactivity to social performance feedback, even when controlling for ED. Given substantial and consistent evidence on hyperactive limbic activity in both BD and BPD, we expect significant differences between both clinical groups and HC subjects, with the former exhibiting elevated activity relative to the latter.

METHODS AND MATERIALS

Participants

A total of 79 participants were originally recruited (54 females). Both patients with BD (n = 18, 8 females) and BPD (n = 24, 23 females) were recruited through a specialized outpatients program of the Geneva University Hospital. BPD psychiatric diagnosis was established using the Structured Clinical Interview for DSM-IV (19). BD diagnosis was established with the Mini-International Neuropsychiatric Interview (20) as part of the standard clinical evaluation. In addition, patients were also interviewed by trained psychologists using the Diagnostic Interview for Genetic Studies (21,22) for the study. Patients with BD (8 BD I, 8 BD II, 2 BD not otherwise specified) were euthymic ($<$6 on Young Mania Rating Scale and $<$12 on Montgomery–Åsberg Depression Rating Scale) and had been on stable medication for at least 4 weeks. HC subjects (n = 37, 23 females) were recruited from the general population in Geneva via web announcements on classified websites, local databases, and flyers distributed in the University of Geneva Medical School. HC subjects participated if reporting no history of psychiatric, neurologic, or psychotherapeutic treatment and no parental history of psychiatric disorders. HC subjects participated if reporting no history of psychiatric, neurologic, or psychotherapeutic treatment, no parental history of psychiatric disorders, and no more than one lifetime mood disorder episode.

Exclusion criteria for all participants were antecedent head trauma and any contraindication for MRI safety prerequisites (e.g., metal objects in body). All participants had normal or corrected-to-normal vision and provided informed consent via a signed consent form. This study was approved by the University of Geneva research ethics committee (CER 13-081).

Experimental Task

The experimental task used our adapted version of the Montreal Imaging Stress Task (23), in which task performance is followed by rest periods. In the Montreal Imaging Stress Task, the participants perform challenging arithmetic calculations in a given time frame while being compared with a fictive control group. Combining such social evaluative threat with uncontrollability reliably produces elevated psychosocial stress that allows for assessing direct reactivity during the task (24). The participants were first asked to perform mental arithmetic calculations in blocks of five trials presented on a computer screen (Figure 1). At the beginning of every trial, a response cursor appeared at a default position of 5 on a horizontal response scale (0–10), and the participants used a button box to move the cursor right or left to select the correct number. Time pressure was induced via a white bar indicating the passage of time with a black line moving from left to right. In each trial, the participants had a maximum of 9 s to select their response. At the end of the fifth trial in the respective block, the participants viewed their performance feedback on the screen (8 s), which could be positive, negative, or neutral (control condition), as well as their ranking with respect to 34 fictitious same-age participants. This ranking could be high (positive condition), low (negative condition), or absent (control condition). The control condition consisted of a single-digit number to be found on the response scale. Positive and negative feedback conditions thus represented the psychosocial stress period.

After feedback, participants were instructed to close their eyes and rest for a recovery period of 90 s, following previously validated designs (25,26). To control for visual movement artifacts stemming from reading the instructions on the screen, however, we discarded the first 5 s of the recovery period. After 90 s, the participants were alerted to reopen their eyes by an acoustic signal. Each performance feedback condition appeared four times for a total of 12 events in two separate sessions, each session lasting 10 to 12 minutes.

Behavioral Measures

During the Montreal Imaging Stress Task, we measured accuracy (percentage of correct answers averaged over the five-trial block for each condition) and reaction time (milliseconds to answer, averaged over the five-trial block in each condition). We ran a 3 $\times$ 3 repeated-measures analysis of variance (ANOVA), using condition (positive, negative, neutral feedback) as a within-subjects factor and diagnosis (BD, BPD, HC) as a between-subjects factor. Statistical analyses were conducted using IBM SPSS Statistics 25 for Windows.

Psychological Measures

We administered the following self-report questionnaires prior to the laboratory visit to measure different trait variables

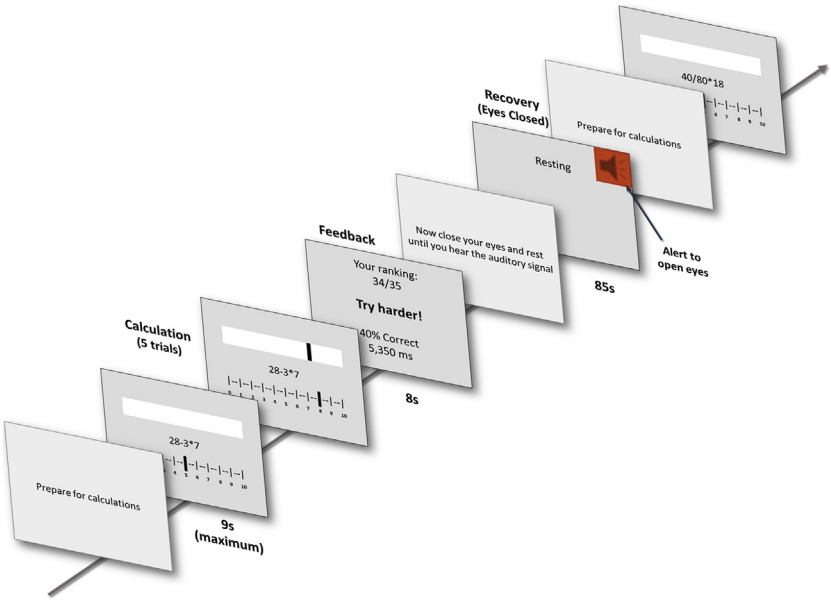

Figure 1. Adapted Montreal Imaging Stress Task [paralleling our previous study (23)]. This example shows the negative condition, where feedback was negative and ranking was low.

associated with ED, i.e., cED, affective lability, and trait anger and anxiety. We assessed cED via the 36-item Cognitive Emotion Regulation Questionnaire, wherein we included only the nonadaptive cognitive emotion regulation subscale (27). Global affective lability was assessed via the Affective Lability Scale, a 54-item scale measuring tendencies in mood shifts between what the individual considers normal to affective domains of anger, anxiety, depression, and elation (28). Trait anger was evaluated via the 22-item trait subscale of the State-Trait Anger Expression Inventory (29). Trait anxiety was measured via the 20-item trait subscale of the State-Trait Anxiety Inventory (30). To control for ED in BPD, we included these four scores as covariates in a subsequent functional MRI (fMRI) analysis.

Psychophysiological Stress Induction Measure

Similar to our recent study (23), we measured heart rate during the recovery period as a psychophysiological marker of sympathetic arousal because increased heart rate indicates successful stress induction (31). Methods and results are provided in the Supplement.

Functional MRI

Functional brain images were acquired with a 3T Magnetom TIM Trio scanner (Siemens) and a 32-channel head coil using a standard echo-planar imaging sequence (36 transverse slices with 20% gap, 64 × 64 base resolution, voxel size: 3.2 × 3.2 × 3.2 mm, repetition time: 2100 ms, echo time: 30 ms, flip angle: 80°, field of view: 192 mm). The MRI data were collected at the Brain and Behaviour Laboratory at the University of Geneva Medical School and computations were performed using high-performance computing at the University of Geneva on the "Baobab" cluster, one of the scientific computing clusters provided by the university.

Preprocessing of the fMRI data was effectuated using the standard procedures implemented in SPM12 (http://www.fil.ion.ucl.ac.uk/spm). Head movement was calculated by computing maximum framewise displacement (32). At the first level, a general linear model of individual fMRI data was designed using eight events with varying durations: five sequential screens of 1) calculations (~45 s maximum) or 2) control calculations (~45 s maximum); three different 8-s feedback periods of 3) positive, 4) negative, or 5) neutral feedback; and three 85-s recovery periods following 6) positive, 7) negative, or 8) neutral feedback.

At the second (group) level, we created a 3 × 3 flexible factorial design for the feedback period testing for condition (positive, negative, neutral feedback) and diagnosis (BD, BPD, HC) with subject as a random-effects factor (33). This was used to assess the main effects of condition (i.e., [positive + negative] > neutral, positive < > negative), diagnosis (BD < > BPD + HC, BPD < > BD + HC, HC < > BD + BPD), and a possible two-way condition × diagnosis interaction.

Second-level analyses and multiple comparison corrections were implemented using SPM12. All results are presented using $p < .05$ cluster-level familywise error corrected (FWEc), with the cluster-forming threshold at voxel-level $p < .001$ (i.e., $p_{FWEc} < .05$). When possible, the correction threshold levels were increased to improve anatomical precision, thus using a stricter cluster-forming threshold at voxel-level $p_{FWE} < .05$ (i.e., $p_{FWE} < .05$). Peak cluster locations of all analyses are reported using the Montreal Neurological Institute coordinates. Areas of neural regions were defined with the aid of the Harvard-Oxford Cortical-Subcortical Structural Atlas (34) and the probabilistic cerebellar atlas (35).

Manipulation Check. Before conducting the fMRI second-level analyses, we controlled for feedback incongruence during the reactivity period because feedback is manipulated to

ensure balanced positive, negative, and neutral conditions, and some participants may have noticed incongruence between their performance and the subsequent feedback. We thus used a 3 × 3 flexible factorial design with congruence (incongruent, congruent, neutral feedback) as a within-subjects factor, diagnosis (BD, BPD, HC) as a between-subjects factor, and subject as a random-effects factor. Congruent feedback corresponded with the participant's performance (e.g., positive feedback after positive performance), whereas incongruent feedback did not correspond with the participant's performance (e.g., positive feedback after negative performance). Positive performance reflected a success rate of 60% or higher on the five calculation trials of the respective block, whereas negative performance reflected 40% or lower on the five calculation trials of the respective block, paralleling our previous study (23). In our analysis, we investigated the contrasts of incongruence and congruence during feedback reactivity.

RESULTS

Six participants were removed for invalid/missing data (e.g., missing MRI data), resulting in a final sample of 73 participants, with 17 patients with BD (8 female), 24 patients with BPD (23 female), and 32 HC subjects (19 females) (Table 1). The age differences between groups were not statistically significant ($F_{2,70} = 0.785$, $p = .460$). A χ^2 analysis of group differences in handedness yielded no significant results ($p = .464$).

Behavioral Measures

To investigate the participants' commitment to the experimental task, performance accuracy was analyzed: 52.50% (±19.76%) of responses were correct for the calculation and 96.44% (±6.26%) were correct for control conditions. The average reaction time was 5835.89 ms (±1249.60 ms) for the calculation and 1888.21 ms (±512.02 ms) for control conditions. We observed a significant main effect of condition for both accuracy ($F_{1,70} = 378.93$, $p < .001$, partial $\eta^2 = 0.844$) and reaction time ($F_{1,70} = 610.17$, $p < .001$, partial $\eta^2 = 0.897$). The accuracy was significantly lower and reaction time was significantly longer in the calculation versus control condition, as expected. There was a significant main effect of diagnosis in both accuracy ($F_{1,70} = 7.208$, $p = .001$, partial $\eta^2 = 0.171$) and reaction time ($F_{1,70} = 4.680$, $p = .012$, partial $\eta^2 = 0.118$). Patients with BPD responded more poorly and slowly than HC subjects across both conditions. There was a significant diagnosis × condition interaction effect for accuracy only ($F_{1,70} = 3.912$, $p = .025$, partial $\eta^2 = 0.101$), where the difference between patients with BPD and HC subjects was greater during calculation than during control conditions (Table 2).

Given gender and performance differences across groups, we complemented our group analysis by controlling for both variables by including them as covariates in a subsequent fMRI analysis.

Psychological Measures

Concerning psychological measures, we conducted a 3 × 4 repeated-measures ANOVA with diagnosis (BD, BPD, HC) as a between-subjects factor and measure (Affective Lability Scale, Cognitive Emotion Regulation Questionnaire, State-Trait Anxiety Inventory, State-Trait Anger Expression Inventory) as a within-subjects factor. We examined the effects of diagnosis and diagnosis × measure interaction using the standardized values of each measure. We observed a main effect of diagnosis ($F_{1,55} = 53.428$, $p < .001$, partial $\eta^2 = 0.660$). Bonferroni-corrected t tests showed BPD to be significantly higher overall than both BD and HC (p values $< .001$). We also observed a significant diagnosis × measure interaction ($F_{5,146} = 2.707$, $p = .020$, partial $\eta^2 = 0.090$), where patients with BD showed no statistical differences from HC subjects for the Cognitive Emotion Regulation Questionnaire and State-Trait Anger Expression Inventory (Table 3).

Psychophysiological Stress Induction Measure

Detailed results for the psychophysiological stress induction measure are provided in the Supplement and provide evidence that stress was successfully induced during the reactivity

Table 1. Demographic and Medical History

Clinical Variables	BD, $n = 17$	BPD, $n = 24$	HC, $n = 32$	Total
Female, *n*	8	23	19	50
Male, *n*	9	1	13	23
Age, Years, Mean (SD)	28.29 (6.17)	26.08 (4.94)	26.38 (6.5)	26.73 (5.94)
Age Range, Years	20–39	18–39	18–39	18–39
Left Handed, *n*	1	0	2	3
Education, Years	14.59	14.71	15.00	14.81
Hospitalizations, Mean, *n*	3.69	2.60	0.04	1.71
Medicated,[a] *n*	13	4	0	17
Substance Abuse, *n*	14	5	3	22
Anxiety/Phobia,[b] *n*	6	18	1	25
ADHD, *n*	6	6	3	15
Age of Onset[c], Years, Mean	18.36	17.41	20.00	18.06

ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; BPD, borderline personality disorder; HC, healthy control.
[a]Psychotropic medication only.
[b]Includes agoraphobia, social anxiety, general anxiety, obsessive-compulsive disorder, panic disorder, and posttraumatic stress disorder.
[c]Concerning mood disorder episodes.

Table 2. Task-Based Performance Variables for BD (*n* = 17), BPD (*n* = 24), and HC (*n* = 32) Groups

Performance	Condition	BD	BPD	HC	Diagnosis Effects	
					Effect Size	*p* Value
Accuracy, %	Calculation	54.26	42.08	59.38	0.148	.004
	Control	96.47	94.58	97.81	0.051	.162
Reaction Time, ms, Mean	Calculation	5883.44	6283.5	5474.92	0.080	.054
	Control	1939.68	2021.49	1760.91	0.052	.152

Accuracy was significantly lower, and reaction time was significantly longer in the calculation condition (total average) than in the control condition (total average). Effect size reflects partial η^2 for between-subjects effects of diagnosis from a one-way analysis of variance with condition (calculation, control) as the dependent factor and diagnosis (BD, BPD, and HC) as the fixed group factor.

BD, bipolar disorder; BPD, borderline personality disorder; HC, healthy control.

period (Figure S1). We did not observe an effect of diagnosis, even when controlling for gender, performance, and ED.

Functional MRI

In our principal analyses, we examined whole-brain blood oxygen level–dependent reactivity to social feedback. We tested the main effects of condition (positive, negative, neutral), diagnosis (BD, BPD, HC), and their interaction. Before this, however, we conducted a manipulation check, using a flexible factorial design for testing the main effects of congruence (incongruent, congruent, neutral feedback) and an effect of a congruence × diagnosis interaction.

Neural Reactivity to Feedback: Manipulation Check. In our manipulation check, we observed a main effect of congruence: incongruent (vs. congruent) feedback elicited significantly greater activity within the dACC, anterior insula, striatum, and occipital lobe ($p_{FWE} < .05$) (Figure S2). We observed no main effect of diagnosis or condition × diagnosis interaction, suggesting no group differences linked to incongruence processing. To ensure that the blood oxygen level–dependent signal retrieved from our analyses could not be explained by incongruence processing, we used these thresholded clusters from the congruence analyses as explicit masks when viewing the effects of condition, thus eliminating the effect of incongruence when comparing social (i.e., positive and negative) to neutral feedback.

Table 3. Psychological Measures for Each Diagnosis Group

Measure	BD	BPD	HC	Diagnosis Effect	
				Effect Size	*p* Value
ALS Total	1.02	1.86	0.45	0.628	<.001
CERQ Nonadapt	37.91	48.92	33.45	0.290	<.001
STAI Trait	43.21	60.09	33.07	0.684	<.001
STAXI Trait	16.38	25.04	17.03	0.378	<.001

Effect size reflects partial η^2 for between-subjects effects of diagnosis from separate one-way analyses of variance with measure (ALS total, CERQ nonadapt, STAI trait, STAXI trait) as the dependent variable and diagnosis (BD, BPD, HC) as the fixed group factor. ALS: BD, *n* = 14; BPD, *n* = 23; HC, *n* = 22. CERQ: BD, *n* = 14; BPD, *n* = 24; HC, *n* = 28. STAI: BD, *n* = 14; BPD, *n* = 23; HC, *n* = 28. STAXI: BD, *n* = 13; BPD, *n* = 24; HC, *n* = 25.

ALS, Affective Lability Scale; BD, bipolar disorder; BPD, borderline personality disorder; CERQ, Cognitive Emotion Regulation Questionnaire; HC, healthy control; STAI, State-Trait Anxiety Inventory; STAXI, State-Trait Anger Expression Inventory.

Neural Reactivity to Feedback: Main Effects. Using an exclusive incongruent > congruent feedback reactivity mask (Figure S2), we observed a robust main effect of condition. Both positive and negative feedback, relative to neutral, elicited significantly greater reactivity in the paracingulate gyrus, orbitofrontal cortex (OFC), anterior insula, superior frontal gyrus, mid cingulate gyrus, temporoparietal junction, precuneus, and lateral occipital cortex ($p_{FWE} < .05$) (Figure S3 and Table S1). These effects thus likely occur independent of incongruence processing and support the findings of our previous study (23).

We also found significant main effects of diagnosis for feedback reactivity irrespective of condition. Compared with patients with BPD and HC subjects, patients with BD showed increased activity within the amygdala, extending to the anterior hippocampus ($p_{FWEc} < .05$) (Figure S4). When controlling for gender and performance (accuracy/reaction time), however, this effect did not survive. Given the important link between limbic hyperactivity and BD (15,36), we subsequently conducted a small-volume correction analysis using this limbic area cluster as a mask when controlling for gender and performance. This, however, revealed no significant difference. Compared with patients with BD and HC subjects, patients with BPD demonstrated hyperactivity in the pregenual ACC, paracingulate gyrus, OFC, anterior insula, striatum (putamen), superior frontal gyrus, dACC, precentral gyrus, supramarginal gyrus, and lateral occipital cortex, activations that survived when controlling for gender and performance (Figure 2A and Table 4). Conversely, when examining hypoactivations, patients with BD showed significantly lower reactivity relative to patients with BPD and HC subjects in several regions, including the dorsolateral PFC, dorsomedial PFC (dmPFC), pregenual ACC, paracingulate gyrus, dACC, anterior insula, OFC, striatum (putamen), and the temporoparietal junction, accounting for gender and performance differences ($p_{FWE} < .05$) (Figure 2B and Table 4). Compared with patients with BPD and BD, HC subjects demonstrated significantly decreased reactivity within the amygdala/hippocampus and thalamus ($p_{FWEc} < .05$) (Figure S5). Although controlling for gender and performance removed these effects, we used these clusters as a mask for a more detailed, subsequent small-volume correction analysis, given the limbic region's relevance to our hypotheses. This revealed significant effects within the amygdala and thalamus ($p_{FWEc} < .05$) (Figure 2C and Table 4). We observed no condition × diagnosis interaction effects.

To examine lower-level group differences, we conducted three 3 × 3 repeated-measures ANOVAs with condition

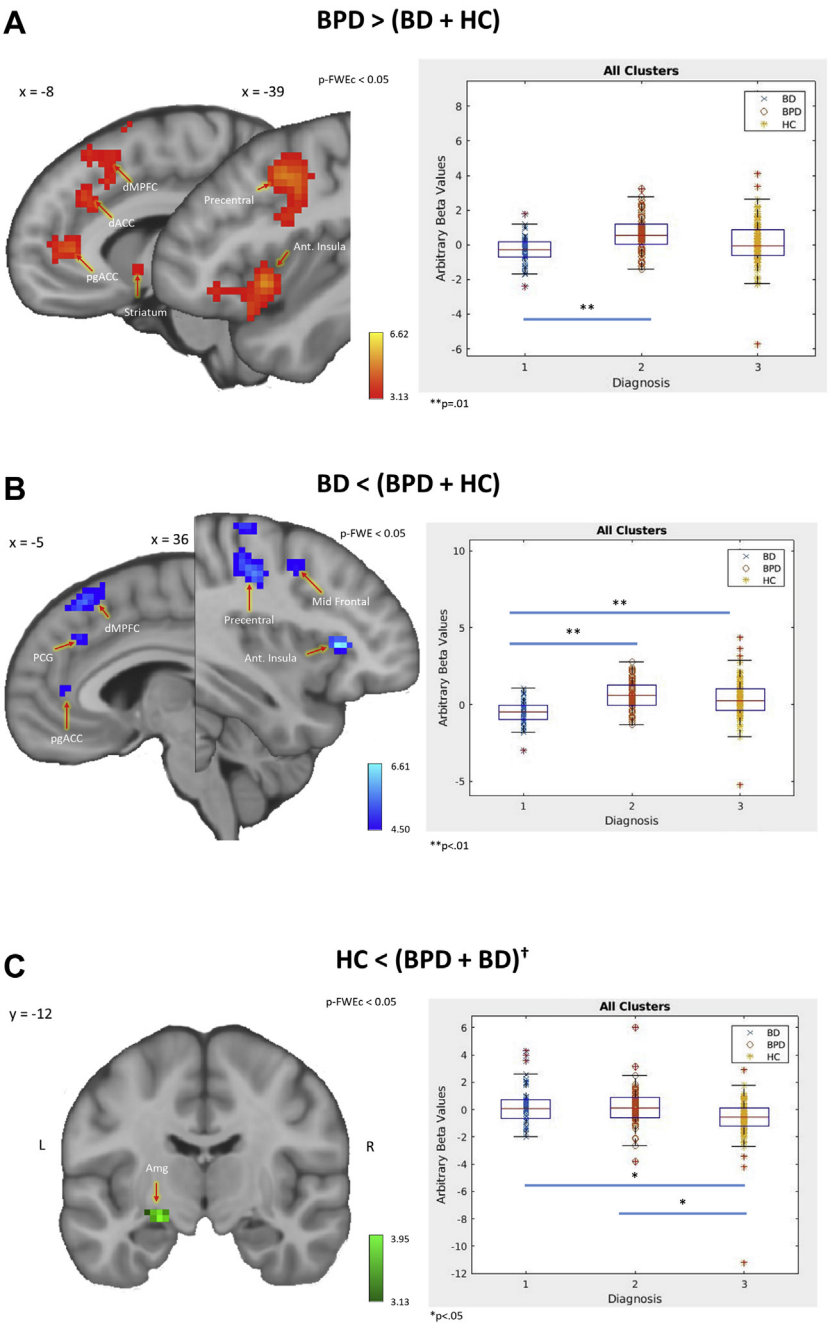

Figure 2. Main effects of diagnosis during feedback reactivity, controlling for gender and performance. Figure illustrates whole-brain blood oxygen level–dependent activations while viewing feedback (positive, negative, neutral), with increased activations in **(A)** patients with borderline personality disorder (BPD) vs. patients with bipolar disorder (BD) and healthy control (HC) subjects ($p_{FWEc} < .05$, k = 118 voxels) with a significant effect of diagnosis whereby BPD yielded significantly greater activity in clusters relative to both patients with BD and HC subjects ($F_{2,216} = 9.487$, $p < .001$, partial $\eta^2 = 0.081$), **(B)** patients with BPD and HC subjects vs. patients with BD ($p_{FWE} < .05$, k = 05) with a significant effect of diagnosis where BD yielded significantly decreased activity in clusters relative to both BPD and HC groups ($F_{2,216} = 13.808$, $p < .001$, partial $\eta^2 = 0.113$), and **(C)** BD and BPD groups vs. HC group ($p_{FWEc} < .05$, k = 02) with a significant effect of diagnosis where HC group demonstrated significantly decreased activity in clusters relative to both BD and BPD groups ($F_{2,216} = 9.818$, $p < .001$, partial $\eta^2 = 0.083$). †Small-volume correction conducted from limbic area gray matter mask retrieved from same contrast but without controlling for gender and performance. All results have been corrected for gender and performance differences between groups. Amg, amygdala; Ant Ins, anterior insula; dACC, dorsal anterior cingulate cortex; dmPFC, dorsomedial prefrontal cortex; FWE, $p < .05$ voxel-level familywise error–corrected; FWEc, $p < .05$ cluster-level FWE-corrected, cluster-forming threshold at voxel-level $p < .001$; PCG, paracingulate gyrus; pgACC, pregenual ACC.

(positive, negative, neutral) as a within-subjects factor and diagnosis (BD, BPD, HC) as a between-subjects factor on beta values of all ensuing clusters for the three contrasts BPD > (BD + HC), BD < (BPD + HC), and HC < (BD + BPD) as the dependent variable. For the purpose of these analyses, we examined diagnosis only. For BPD > (BD + HC), there was a significant effect of diagnosis ($F_{2,70} = 4.669$, $p = .012$, partial $\eta^2 = 0.118$), where cluster activations were significantly higher in patients with BPD than BD ($p = .010$, Games-Howell corrected for nonhomogeneous variances). For BD < (BPD + HC), there was a significant effect of diagnosis ($F_{2,70} = 6.626$, $p = .002$, partial $\eta^2 = 0.159$), where cluster activations were significantly lower (Bonferroni-corrected) in patients with BD than BPD ($p = .003$) and HC subjects ($p = .009$). Finally, for (BD + BPD) > HC, there was a significant effect of diagnosis ($F_{2,70} = 5.650$, $p = .005$, partial $\eta^2 = 0.139$), where amygdala and thalamus activations were significantly lower (Bonferroni-corrected) in HC subjects than in BD ($p = .016$) and BPD

Table 4. Main Effects of Diagnosis During Feedback Reactivity, Controlling for Gender and Performance

Activation Condition	Cluster	Subcluster	Hem	*k*	T	x	y	z
BPD > (BD + HC)	Orbitofrontal cortex		L	465	6.62	−24	27	−9
		Anterior insula	L		5.23	−39	12	−6
		Striatum (putamen)	L		5.17	−18	3	−12
	Superior frontal gyrus		R	454	5.89	12	24	63
		Dorsal ACC	R		4.66	6	24	24
		Superior frontal gyrus	L		4.53	−21	12	66
	Lateral occipital cortex		L	118	5.19	−27	−69	36
		Lateral occipital cortex	L		4.64	−18	−66	36
		Lateral occipital cortex	L		3.55	−15	−66	51
	Precentral gyrus		L	303	5.05	−39	3	42
		Precentral gyrus	L		4.53	−42	3	24
		Precentral gyrus	L		4.46	−27	−6	48
	Pregenual ACC		L	184	4.79	−6	42	9
		Pregenual ACC	R		4.42	9	39	9
		Paracingulate gyrus	R		4.27	12	45	0
	Supramarginal gyrus		R	543	4.76	63	−42	21
		Precentral gyrus	R		4.68	45	0	33
		Precentral gyrus	R		4.51	42	−21	63
BD < (BPD + HC)	Frontal operculum/anterior insula		R	23	6.61	36	24	6
	Lateral occipital cortex		R	42	6.37	27	−63	36
	Supramarginal gyrus		L	138	6.21	−51	−42	33
		Supramarginal gyrus	L		5.3	−54	−45	45
		Postcentral gyrus	L		5.07	−36	−30	39
	Supramarginal gyrus		R	67	6	54	−42	45
	Precentral gyrus		R	89	5.82	36	−18	42
		Precentral gyrus	R		5.55	39	−21	63
	Superior frontal gyrus/dmPFC		R	154	5.74	12	27	63
		Superior frontal gyrus/dmPFC	L		5.64	−6	30	54
		Superior frontal gyrus/dmPFC	R		5.57	12	18	66
	Orbitofrontal cortex		L	25	5.7	−24	21	−9
		Orbitofrontal cortex	L		5.4	−27	30	−12
	Lateral occipital cortex		L	7	5.64	−51	−72	12
	Mid frontal gyrus/dlPFC		R	71	5.48	51	9	30
		Mid frontal gyrus/dlPFC	R		5.4	39	3	45
	Mid frontal gyrus/dlPFC		L	32	5.48	−39	6	45
	Frontal pole/dlPFC		R	12	5.36	45	48	9
	Superior frontal gyrus		L	10	5.21	−12	12	66
	Lateral occipital cortex		L	14	5.21	−27	−66	39
	Precentral gyrus		R	11	5.18	15	−27	72
	Paracingulate gyrus		L	12	5.13	−6	33	36
	Temporoparietal junction		R	40	5.13	57	−30	21
		Supramarginal gyrus	R		5.03	63	−42	21
		Temporoparietal junction	R		4.95	51	−27	12
	Dorsal ACC		R	11	5.07	3	27	27
	Frontal pole/dmPFC		R	5	5.04	6	48	45
	Lateral occipital cortex		L	10	5.02	−42	−72	−15
		Lateral occipital cortex	L		4.72	−48	−66	−18
	Lateral occipital cortex		L	5	5.02	−42	−84	6
	Striatum (putamen)		L	5	5	−18	3	−12
	Mid frontal gyrus/dlPFC		R	5	4.98	51	24	36
	Cuneus		R	5	4.94	6	−87	24
	Paracingulate gyrus		R	7	4.76	9	36	36
	Pregenual ACC		L	6	4.62	−6	39	9

Table 4. Continued

Activation Condition	Cluster	Subcluster	Hem	*k*	T	x	y	z
HC < (BPD + BD)[a]	Amygdala		L	30	3.95	−21	−12	−12
	Thalamus		R	2	3.36	6	−3	−3

Table illustrates statistics of whole-brain BOLD activations while viewing feedback (positive, negative, neutral), with increased activations in BPD vs. BD and HC (cluster-level FWE-corrected $p < .05$, $k = 118$ voxels), BPD and HC vs. BD (cluster-level FWE-corrected $p < .05$, $k = 05$), and BD and BPD vs. HC (cluster-level FWE-corrected $p < .05$, $k = 02$). All results have been corrected for gender and performance differences between groups.

ACC, anterior cingulate cortex; BD, bipolar disorder; BOLD, blood oxygen level–dependent; BPD, borderline personality disorder; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; FWE, familywise error; HC, healthy control; hem, hemisphere; *k*, voxel extent threshold; L, left; R, right; T, peak-level *t* statistic.

[a]Small volume correction conducted from limbic area gray matter mask retrieved from same contrast when not controlling for gender and performance.

($p = .025$). This suggests lower limbic feedback reactivity in HC subjects compared with both clinical groups when controlling for gender and performance.

Neural Reactivity to Feedback: Controlling for ED. To exclude potential confounders from ED, we additionally controlled for affective lability, anger, anxiety, and cED, including them as covariates with gender and performance. Despite this, we continued to observe significant main effects of diagnosis across all three feedback conditions, where BPD exhibited significant hyperactivity relative to both patients with BD and HC subjects in the mid frontal gyrus/dmPFC, precentral gyrus/dorsolateral PFC, OFC, striatum, and anterior insula ($p_{FWEc} < .05$) (Figure 3A and Table 5). Imputing average beta values of all hyperactive clusters in 3 × 3 repeated-measures ANOVA, with condition as within-subject and diagnosis as between-subject factors, yielded a significant effect of diagnosis ($F_{2,55} = 9.074$, $p < .001$, partial $\eta^2 = 0.248$) where activations in patients with BPD were different significantly (Bonferroni-corrected) from those with BD ($p = .003$) and marginally from HC subjects ($p = .052$) (Figure 3A and Table 5).

Conversely, BD exhibited significant and extensive hypoactivations relative to patients with BPD and HC subjects in the frontal pole, dorsolateral PFC, ventrolateral PFC, pregenual ACC, OFC, superior frontal gyrus/dmPFC, anterior insula, inferior frontal gyrus, mid frontal gyrus, postcentral gyrus, the Heschl's gyrus, temporoparietal junction, superior parietal lobule, angular gyrus, and lateral occipital cortex ($p_{FWE} < .05$) (Figure 3B and Table 5). Repeated-measures ANOVA yielded a significant effect of diagnosis ($F_{2,55} = 10.101$, $p < .001$, partial $\eta^2 = 0.269$) where BD activity within these clusters was significantly lower (Games-Howell corrected) than that in patients with BPD ($p < .001$) and HC subjects ($p = .005$) (Figure 3B and Table 5). Finally, HC subjects exhibited significantly greater fusiform activity extending into the lingual gyrus relative to both patients with BD and BPD ($p_{FWEc} < .05$) (Figure 3C and Table 5).

Sensitivity Analysis

Given the imbalance of medicated patients with BD relative to patients with BPD, we conducted post hoc sensitivity analyses (37) to verify the robustness of the main effect of diagnosis on beta values resulting from the contrasts BPD > (BD + HC) and BD < (BPD + HC) when accounting for gender, performance, and psychological measures (see the Supplement). The results revealed low sensitivity of both models to an unobserved confounder, suggesting that our estimated effect of diagnosis on neural reactivity was robust to a single confounder (e.g., medication) in both contrasts.

DISCUSSION

This study attempted to provide a clearer assessment of BPD-specific neural stress reactivity independent of ED by using psychosocial stress induction in fMRI, including an ED disorder clinical group (BD), and providing a thorough measurement of ED-relevant domains (affective lability, anger, anxiety, cED). Here, we show that patients with BPD exhibit hyperactive corticolimbic stress response during feedback reactivity periods, regardless of the condition and relative to patients with BD and HC subjects, when controlling for gender, behavioral performance differences, and ED. Conversely, patients with BD exhibited extensive hypoactive neural stress responding across all feedback conditions, relative to patients with BPD and HC subjects. Finally, HC subjects showed significantly less limbic stress responding, relative to patients with BPD and BD, although this difference may be explained by ED because we saw no significant differences when controlling for ED. Together, these findings suggest consistent patterns of neural stress responding in self- and emotion-regulatory neural regions in patients with BPD and BD that cannot be explained by ED trait differences. This may signify neural traits associated with stress response specific to BPD and BD and not generalizable to ED characteristics per se.

Neural Hyperactivity in BPD

Our results illustrate elevated neural sensitivity to feedback in BPD, regardless of valence, in corticolimbic areas, extending the literature showing BPD corticolimbic hyperarousal to social stimuli (38), particularly when threatened with social rejection (39). Paralleling our findings, patients with BPD show elevated dACC and dmPFC response when presented with social exclusion (6). Thus, irrespective of its valence, performance feedback may invoke rejection-related fears in BPD, eliciting corticolimbic hyperactivity. These neurobiological findings support physiological meta-analytic evidence pointing to a BPD-specific reduction of cortisol suppression of psychosocial stress reactivity (9), which likely associates with dysregulated medial frontal stress response (10).

However, our finding showing BPD stress hyperactivity extending to positive and neutral feedback contradicts earlier stress research in BPD, which showed context-dependent subjective emotional responding in BPD specific to negative feedback relative to clinical controls (40). Still, it extends

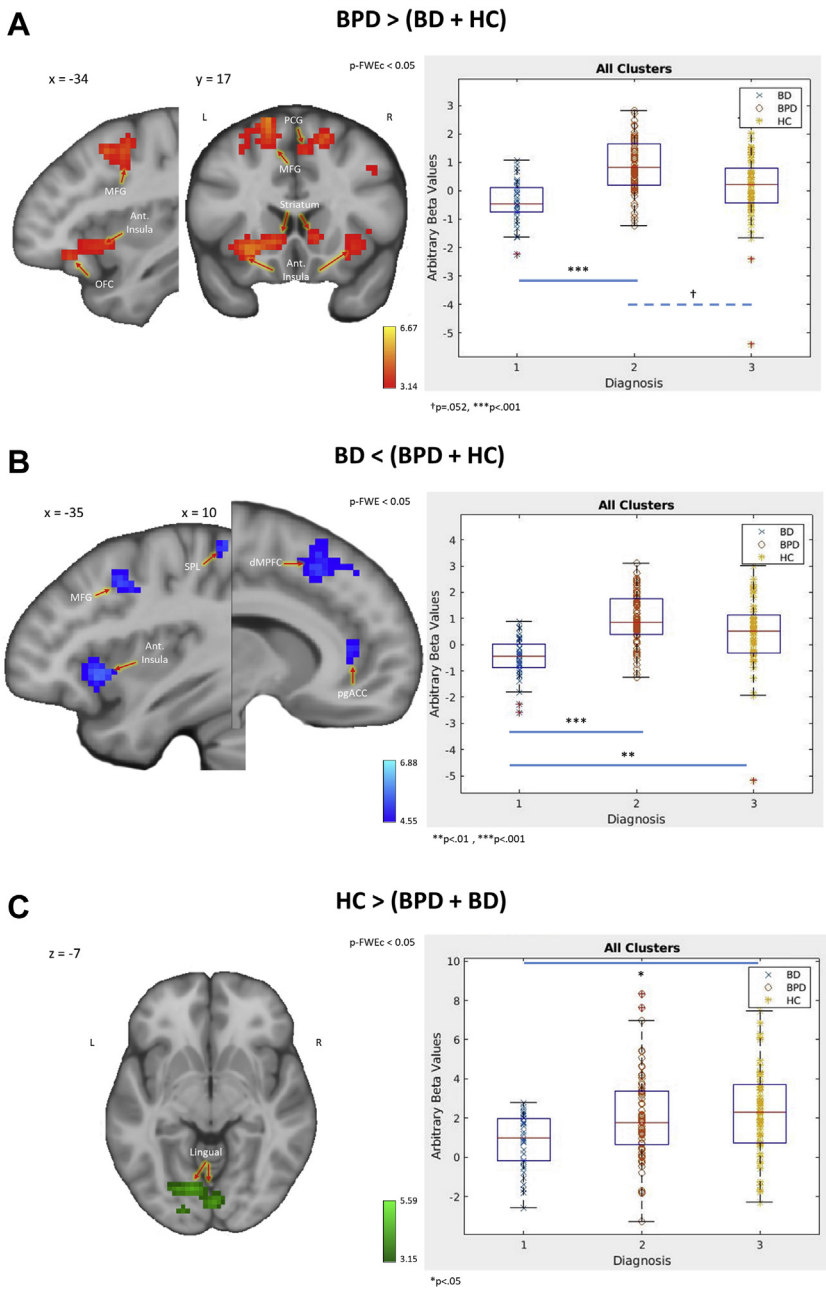

Figure 3. Main effect of diagnosis during feedback reactivity period, controlling for gender, performance, and emotion dysregulation. Figure illustrates whole-brain blood oxygen level–dependent (BOLD) activations while viewing feedback (positive, negative, neutral). **(A)** Overlay shows borderline personality disorder (BPD) BOLD activations relative to both bipolar disorder (BD) and healthy control (HC) groups ($p_{FWEc} < .05$, $k = 133$ voxels). Boxplot figure shows a significant effect of diagnosis ($F_{2,55} = 9.074$, $p < .001$, partial $\eta^2 = 0.248$) in global beta values of activated clusters, with increased activations in BPD group being different significantly from the BD group ($p = .003$) and marginally from the HC group ($p = .052$). **(B)** Overlay of BOLD deactivations of the BD group relative to BPD and HC groups ($p_{FWE} < .05$, $k = 05$). Boxplot figure shows a significant effect of diagnosis ($F_{2,55} = 10.101$, $p < .001$, partial $\eta^2 = 0.269$) in global beta values, where BD demonstrated significantly decreased activity in clusters relative to the BPD group ($p < .001$) and the HC group ($p = .005$). **(C)** Overlay of HC BOLD activations relative to both BD and BPD ($p_{FWEc} < .05$, $k = 247$). Boxplot figure shows a significant effect of diagnosis ($F_{2,55} = 3.358$, $p < .042$, partial $\eta^2 = 0.109$) in global beta values, where the HC group demonstrated significantly increased activity in clusters relative to the BD group ($p = .038$). All results have been corrected for gender, performance, and emotion dysregulation differences between groups. Ant Ins, anterior insula; dmPFC, dorsomedial prefrontal cortex; FWE, $p < .05$ voxel-level familywise error–corrected; FWEc, $p < .05$ cluster-level FWE-corrected, cluster-forming threshold at voxel-level $p < .001$; MFG, mid frontal gyrus; OFC, orbitofrontal cortex; pgACC, pregenual anterior cingulate cortex.

empirical evidence that suggests rejection-related fears may generalize to nonthreatening social information. For example, individuals with BPD show difficulty distinguishing rewarding from nonrewarding social information (41), often misinterpreting neutral social information as hostile (38,42). The ambivalence between negative and neutral stimuli relates to ACC, amygdala, and striatal dysfunction (43), supporting our findings. Thus, BPD neural hyperactivity to performance feedback may generalize to positive and neutral feedback.

Contrary to our neuroimaging findings, we observed no differences in heart rate between patients with BPD and HC subjects. Although this could support meta-analytic findings showing null-to-small effects in overall emotional physiological reactivity in patients with BPD versus HC subjects (44), it may nonetheless relate to important heterogeneity within BPD samples (44). Indeed, the literature demonstrates variations in BPD personality profiles (45), suggesting important interindividual differences in BPD stress responding (46). Although outside the scope of this study, future research would benefit from assessing interindividual differences in ED and their interaction with feedback physiological reactivity in patients with BPD and BD and HC subjects.

Table 5. Main Effect of Diagnosis During Feedback Reactivity Period, Controlling for Gender, Performance, and Emotion Dysregulation

Activation Condition	Cluster	Subcluster	Hem	*k*	T	x	y	z
BPD > (BD + HC)	Orbitofrontal cortex		R	133	6.67	27	24	−12
		Frontal operculum	R		3.26	42	21	6
	Orbitofrontal cortex		L	350	5.84	−27	30	−9
		Striatum (putamen)	L		5.52	−21	21	−6
		Striatum (caudate)	R		4.7	6	9	0
	Mid frontal gyrus		L	480	5.34	−36	3	48
		Superior frontal gyrus/dmPFC	L		5.16	−15	18	66
		Mid frontal gyrus	L		4.63	−33	12	48
	Precentral gyrus		R	150	4.6	42	6	24
		Mid frontal gyrus	R		4.18	42	6	33
		Inferior frontal gyrus/dlPFC	R		3.8	51	12	12
BD < (BPD + HC)	Superior frontal gyrus		L	112	6.88	−12	21	54
	Superior frontal gyrus		L		4.82	−6	36	54
	Frontal pole/vlPFC		R	11	6.86	30	39	−12
	Superior frontal gyrus/dmPFC		R	121	6.24	15	27	54
		Superior frontal gyrus/dmPFC	R		5.58	18	18	57
		Superior frontal gyrus/dmPFC	R		5.45	9	24	48
	Mid frontal gyrus/dlPFC		L	67	6.11	−39	6	45
		Precentral gyrus	L		5.43	−33	3	39
		Mid frontal gyrus	L		4.82	−33	12	48
	Superior parietal lobe		L	33	6.08	−33	−48	63
	Anterior insula		L	65	5.77	−36	18	−6
	Temporoparietal junction		R	60	5.75	51	−39	39
	Lateral occipital cortex		L	14	5.53	−51	−72	15
	Frontal pole/dlPFC		R	9	5.4	45	48	9
		Frontal pole/dlPFC	R		5.02	51	39	12
	Orbitofrontal cortex		L	12	5.35	−27	30	−9
	Pregenual anterior cingulate		L	70	5.3	−3	39	9
		Pregenual anterior cingulate	L/R		5.27	0	39	18
		Pregenual anterior cingulate	R		5.26	9	39	9
	Frontal operculum/anterior insula		R	20	5.2	36	24	6
		Anterior insula	R		4.93	39	21	−3
	Inferior frontal gyrus		R	27	5.15	51	15	30
	Postcentral gyrus		R	17	5.11	39	−24	66
	Heschl's gyrus		L	7	5.03	−45	−27	6
	Mid frontal gyrus		R	17	4.97	33	3	48
	Superior parietal lobe/angular gyrus		R	12	4.93	36	−54	51
		Superior parietal lobe/angular gyrus	R		4.69	27	−60	48
	Lateral occipital cortex		L	5	4.86	−42	−72	−15
	Lateral occipital cortex		R	6	4.75	30	−63	36
HC > (BD + BPD)	Fusiform gyrus		L	247	5.59	−33	−75	−15
		Fusiform gyrus	L		4.67	−24	−75	−3
		Fusiform gyrus	L		4.57	−21	−75	−12

Table illustrates whole-brain BOLD responding while viewing feedback (positive, negative, neutral). BPD vs. BD and HC (FWEc-corrected $p < .05$, $k = 133$ voxels); BPD and HC vs. BD (FWE-corrected $p < .05$, $k = 05$); HC vs. BD and BPD (FWEc-corrected $p < .05$, $k = 247$). All results have been corrected for gender, performance, and emotion dysregulation differences between groups.

BD, bipolar disorder; BOLD, blood oxygen level–dependent; BPD, borderline personality disorder; dlPFC, dorsolateral prefrontal cortex; dMPFC, dorsomedial prefrontal cortex; FWE, familywise error; FWEc, cluster-level FWE; HC, healthy control; hem, hemisphere; *k*, voxel threshold; L, left; R, right; T, peak-level *t* statistic; vlPFC, ventrolateral prefrontal cortex.

Neural Hypoactivity in BD

Patients with BD showed varying activation patterns, with hypoactivity in dorsal cognitive control regions and hyperactivity in limbic affective regions, although the latter may be more sensitive to gender and performance differences. Nonetheless, these findings parallel the current neural model of BD, explaining affective disturbances as a result of damped inhibitory control over elevated affective reactivity (15,36). Moreover, the literature shows that patients with euthymic BD exhibit neuropsychological impairments related to inhibitory control and selective attention (17), suggesting an inability to inhibit intrusive cognitions. Together, our findings reveal extensive dampening of dorsal regulatory regions relative to patients with BPD and HC subjects that may be specific to euthymic BD and independent of ED traits.

Limitations

Although the ED measures conducted in this study have been validated empirically, they are nonetheless limited to subjective self-reporting. Objective assessment of ED is thus limited here and would require further behavioral testing in ED clinical groups. In addition, because we did not observe the effects of an interaction in our fMRI data, low-level group differences (e.g., BPD $>$ HC) should be considered with caution and more as descriptive than conclusive (47). These warrant future investigation, nonetheless. Moreover, as the sample size was limited, larger and more gender-balanced samples might allow for increased variance in interindividual traits and increased likelihood of interaction effects.

Conclusions

These results reveal increased corticolimbic reactivity during psychosocial stress in patients with BPD compared with an ED disorder clinical control group and HC subjects, even when controlling for ED. We believe that these results provide a clearer assessment of BPD neural stress responding when considering ED traits and thus show hyperactive corticolimbic psychosocial stress reactivity to likely occur in BPD as a function of disease-specific traits rather than shared ED features. These results thus highlight the importance of considering BPD as a clinical diagnostic profile distinguishable from other ED disorder groups.

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The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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