Neural Processing of Emotional Overinvolvement in Borderline Personality Disorder

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Objective: Patients with borderline personality disorder (BPD) fare better clinically if their families are rated as being high in emotional overinvolvement, which is characterized by marked emotionality, anxious concern, and protective behavior. This is not true of patients with disorders such as schizophrenia or major depression. We used functional magnetic resonance imaging methods to explore the link between emotional overinvolvement (EOI) and better clinical outcome in BPD. Specifically, we tested the hypothesis that, unlike healthy controls or people with other psychiatric problems, people with BPD process EOI as an approach-related stimulus.

Method: Participants with BPD (n = 13) and dysthymia (n = 10) (*DSM-IV* criteria for both) and healthy controls (n = 11) were imaged using a high field strength (3T) scanner while they listened to a standardized auditory stimulus consisting of either 4 neutral or 4 EOI comments. Participants also rated their mood before and after exposure to the comments.

Results: All participants reported increased negative mood after hearing EOI and rated the EOI comments as negative stimuli. However, after subtracting activation to neutral comments, participants with BPD showed higher activation in left prefrontal regions during EOI compared to the other groups. Increased left prefrontal activation during EOI was also correlated with clinical measures indicative of borderline pathology. Participants with dysthymia showed increased amygdala activation during EOI. This was not true for the healthy controls or participants with BPD.

Conclusions: For people with BPD, EOI may be activating neural circuitry implicated in the processing of approach-related stimuli. Increased left prefrontal activation to EOI may be a vulnerability marker for BPD. These findings may also help explain why BPD patients do better clinically in high EOI family environments.

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Expressed emotion is a measure of the family environment that has been reliably associated with relapse in patients suffering from a range of Axis I disorders.[1,2] One component of the expressed emotion measure, termed *emotional overinvolvement* (EOI), is characterized by high levels of emotional concern and anxiety as well as self-sacrificing or overprotective attitudes and behaviors toward patients. For those diagnosed with schizophrenia and mood disorders, high levels of family EOI are associated with patients doing worse over the course of a 9- to 12-month follow-up period.[1]

For patients with borderline personality disorder (BPD), however, the opposite appears to be true. Hooley and Hoffman[3] reported that patients with BPD did better clinically over the course of a 1-year follow-up if their close relatives showed higher rather than lower levels of EOI. The association between EOI and better clinical outcome in BPD also remained when other characteristics of patients that were predictive of a better prognosis were controlled statistically. Although this finding remains in need of replication, available evidence suggests that, rather than being a risk factor for relapse, EOI may be protective against poor clinical outcome for patients suffering from BPD.

Why should patients with BPD do better if their relatives show high levels of EOI? Emotionally overinvolved statements are statements that reflect high levels of concern, anxiety, and worry about the patient (eg, "This is tearing me apart. I am sick with worry about that girl."). One possibility is that high levels of EOI provide a form of emotional gratification for BPD patients. In a condition characterized by interpersonal concerns and fears of abandonment, EOI comments could provide some form of validation[4] and be seen as evidence of caring rather than as evidence of excessive intrusiveness or enmeshment.

This study used both self-report and functional magnetic resonance imaging (fMRI) methods to examine how patients with BPD process EOI comments. Although neuroimaging studies of BPD are still in their infancy, dysfunctions in frontolimbic circuitry have been hypothesized to underlie some of the emotion regulation problems characteristic of people with this disorder.[5,6] Evidence suggests that BPD patients may be characterized by enhanced amygdala activation (relative to controls) to highly arousing and unpleasant emotional stimuli such as slides of mutilated bodies[7] or neutral, sad, or fearful faces.[8] Patterns of prefrontal activation may also be different in people who have BPD compared to people without BPD. However, no consistent

findings have yet been reported across studies.[9,10] This may reflect sample differences or differences in the tasks that are employed.

The interpretation of the results of some investigations is further complicated by the type of control samples that are used. For example, 70% of the control subjects in the study of Schmahl et al[10] had past histories of psychiatric problems such as major depression, posttraumatic stress disorder (PTSD), drug and alcohol abuse, or eating disorders. However, even when they are fully recovered, people who have past histories of psychopathology respond differently to affective challenges than those who have never had an Axis I disorder.[11,12] A necessary first step, therefore, is to compare brain activation in participants with BPD to controls with no current or past psychopathology, as well as to carefully diagnosed psychiatric comparison groups.

In this investigation, the activation patterns of BPD patients to neutral and EOI-type auditory stimuli were compared with activation patterns of both healthy controls and people with dysthymia. One advantage of auditory stimuli is that, unlike visual stimuli, they cannot be avoided in a scanning environment by averting gaze.[13,14] Participants with dysthymia were selected as a psychiatric comparison group because chronic negative affect is highly characteristic of BPD sufferers[15] and because mood disorders are highly comorbid with BPD.[16,17]

On the basis of the previously demonstrated link between EOI and better clinical outcomes, we hypothesized that BPD participants would process EOI as an approach-related stimulus. More specifically, we predicted that they would show greater activation in left prefrontal cortex during exposure to EOI remarks than either participants with dysthymia or healthy controls. This prediction was based on the work of Davidson[18] implicating the left prefrontal cortex in the "maintenance of reinforcement-related behavioral approach"[(p.383)] as well as electroencephalogram and imaging studies that have linked left prefrontal activation to positive emotional stimuli and reward processing.[19–23] For example, using fMRI, Canli and colleagues[21] reported increased left-sided activation to positive emotional images and increased right-sided activation to negative emotional images in a sample of healthy female participants. In another fMRI study,[22] positively valenced social stimuli were found to be associated with greater activation in left prefrontal cortex in both healthy controls and remitted depressed patients. A positron emission tomography study by Thut and colleagues[23] has also demonstrated increased regional cerebral blood flow in left dorsolateral prefrontal cortex when healthy controls received a monetary reward.

In addition to the prediction about left prefrontal activation, we further hypothesized that amygdala activation in BPD participants during EOI would be comparable to that of controls. On the basis of our previous work on depression, we also anticipated that participants with dysthymia would show elevations in amygdala activation during EOI relative to participants in the other 2 groups.[12,24] Although increased amygdala activity has been found to be associated with exposure to negative stimuli in people with BPD,[7,8] our predictions were based on the empirical data linking EOI with relapse in depression but with a more favorable clinical outcome in BPD.[3]

METHOD

Participants

Participants were recruited by means of advertisements in local media. All potential participants received an initial screening interview conducted by telephone. Those who appeared likely to meet study criteria and were also free of neurologic problems and history of head trauma were invited for a further diagnostic assessment with a trained and experienced clinician (J.M.H.).

Clinical assessments were conducted using the patient edition of the Structured Clinical Interview for *DSM-IV* (SCID)[25] and the SCID-II.[26] To qualify as a healthy control, participants had to be free of current or past Axis I or Axis II psychopathology. For the BPD study group, participants were required to meet *DSM-IV* criteria[27] for BPD (ie, at least 5/9 symptoms). Medication use or the presence of other Axis I or Axis II disorders were not exclusion criteria for entry to the BPD group. A psychiatric control sample of participants with dysthymia was also recruited. All participants with dysthymia were required to meet *DSM-IV* criteria for the disorder and to have no other current Axis I or Axis II diagnoses. In addition, participants were excluded from the dysthymia group if they endorsed *any DSM-IV* symptoms of BPD. As with the BPD study group, medication use was not an exclusion criterion for entry into the dysthymia group.

The final sample consisted of 34 right-handed female participants aged 19–35 years (mean, 25.21; SD = 4.48). Of these, 13 were diagnosed with BPD, 10 were diagnosed with dysthymia, and 11 were healthy controls with no current or past history of psychopathology. All were college educated or were currently students in college. The groups did not differ in age, ($F_{2,31} = 0.47$, NS). Five of the 13 BPD participants (38%) were currently suffering from current major depressive disorder in addition to BPD and almost all (12/13 or 92%) reported a past history of major depression. No participant with BPD had a current or past history of PTSD, although as might be expected, other clinical problems (eating disorders, social phobia, dysthymia, and past drug and alcohol abuse) were not uncommon. Six of the 10 participants with dysthymia (60%) had past histories of major depression. However, none had any current Axis I disorder apart from dysthymia. Ten of the BPD participants (77%) and 5 (50%) of the participants with dysthymia were taking antidepressant medications All participants provided written informed consent and the study was approved by the Committee on the Use of Human Subjects at Harvard University and at McLean Hospital.

Procedure

Prior to scanning, participants completed the Beck Depression Inventory (BDI),[28] the anhedonia and anxious

arousal subscales of the Mood and Anxiety Symptom Questionnaire (MASQ)[29] as well as the trait forms of the Positive and Negative Affect Schedule (PANAS).[30] Participants also completed the Schedule for Nonadaptive and Adaptive Personality (SNAP),[31] a 375-item, true/false questionnaire designed to measure traits associated with personality disorders.

Measures of positive and negative mood using the state form of the PANAS were also obtained from participants after they entered the scanner, after localizing scans had been completed, after hearing neutral comments, as well as after they had been exposed to other experimental conditions that are not the subject of this report. PANAS mood ratings were also collected before and after participants had been exposed to the EOI challenge stimulus. When the scanning session was over, participants reviewed the neutral and the EOI comments and rated the valence of each comment on a 1–9 scale (from "very positive" to "very negative"). Participants also rated the level of emotional arousal the comments generated for them (1–9 scale; from "not at all arousing or emotionally stimulating" to "very arousing and emotionally stimulating") and provided ratings of how personally relevant they felt each neutral or EOI comment was for them (1–9; from "did not at all feel this was about me" to "totally felt this was about me").

EOI Challenge

While they were in the scanner, participants were exposed to a standardized auditory challenge stimulus presented in a block design. The auditory challenge stimulus consisted of 4 separate EOI comments. These comments were written by the senior author (J.M.H.) and were based on actual comments that had been made by relatives of patients with BPD in a previous investigation.[3] In this respect, the EOI challenge stimuli were specifically designed to be both valid and appropriate for use in a neuroimaging protocol.

The EOI comments were recorded onto a compact disk for presentation within the magnetic environment. Participants heard the comments through gradient damping headphones, which are part of the integrated audio/video system for use with magnetic resonance systems. The same female voice was used in the recording of each comment. All comments lasted 20 seconds and were preceded and followed by a 20 second rest period during which the participant heard silence. All comments were phrased in the third person, and participants were asked to listen to each comment as if it were being said about them. The following is an example of 1 of the EOI comments that was used: "One thing that especially worries me about her is how fragile she is emotionally. She's had a huge amount of emotional pain in her life and it just destroys me to think about how much that poor girl suffers. If I could suffer instead of her and take away some of the pain, I would do it. It tears me up to see her the way that she is."

Neutral Comments

To provide a comparison condition we also exposed our participants to neutral auditory comments. Like the EOI comments, the neutral comments were said in the third person and recorded using the same female voice. Participants heard a total of 4 comments, each lasting 20 seconds. The neutral comments described routine daily activities, as in the following example: "One of the things she did today was to go out to lunch. She decided to go out for a sandwich and a cup of coffee around noon. She got there before the place got busy so it was pretty easy for her to find an empty table. She was there for about half an hour. She ate her sandwich, drank her coffee and read the newspaper. By the time she left, the place was quite crowded."

Functional MRI Data Acquisition

All scanning was performed on a 3.0 Tesla Siemens MR scanner (Siemens Medical Solutions, Malvern, Pennsylvania). Using a quadrature head-coil, high-resolution echoplanar images were acquired during baseline and recovery conditions throughout the presentation of the neutral and EOI stimuli. Slices were acquired at a thickness of 5 mm, with a 0 mm skip between slices for the entire brain. Images were collected every 3 seconds (repetition time [TR] = 3,000) using a single-shot, gradient pulse-echo sequence (echo time [TE] = 30 milliseconds, flip angle = 90 degrees); 50 images per slice. An image matrix of 64 × 64 was used with a 3 mm by 3 mm in-plane resolution. Both matched T1 and T2 echo planar imaging image sets were also acquired for each subject (T1: matrix size = 2,562, flip = 90°, TR = 5,760; TE = 80 ms, number of shots = 4; T2: matrix size = 2,562, flip = 90°, TR = 6,680; TE = 75 ms, number of shots = 4). Head cushions as well as paper tape placed across the forehead and underneath the chin served as a reminder to participants to limit head motion during scanning. Scan landmarks were also checked for each participant at the conclusion of each scan.

Preprocessing

Images were realigned and corrected for motion using an intrarun realignment algorithm in statistical parametric mapping (SPM) 5. Functional magnetic resonance imaging data were convolved into 3-dimensional space and smoothed using an isotropic Gaussian kernel (full width half maximum = 10 mm), and resliced to 2 × 2 × 2 mm within Montreal Neurological Institute space using sinc interpolation. Statistical analysis for individual subjects was performed applying the framework of the general linear model[32,33] using a boxcar reference function convolved with the hemodynamic response function. Contrasts were set to test for voxel-wise effects of signal differences between conditions and statistical parametric maps (SPM{t}) were calculated for each subject.

Statistical Analysis

Individual contrast images were entered into a fixed-effects multiple regression model. Activation during the block of EOI commentary was contrasted with activation during the neutral condition. This procedure yielded statistical parametric maps that isolated the activity unique to exposure to EOI. Finally, using a random-effects *t* test analysis, we made direct comparisons between the BPD and

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dysthymia study groups and between the borderline and healthy control study groups. For the present study, our hypotheses were constrained to specific cortical and limbic regions believed to be sensitive to affective processing (superior frontal cortex and amygdala). The region of interest masks were created using the Wake Forest University Pickatlas utility[34,35] and excluded activity in nonhypothesized regions, permitting adjustment of statistical thresholds using the small volume correction implemented in SPM 5. The statistical height threshold was set at $P < .05$. Only active clusters with a minimum extent (k) threshold of 10 contiguous voxels were considered significant.

RESULTS

Self-Report Clinical Assessments

Immediately prior to scanning, participants completed several self-report measures of depression and anxiety. One-way analyses of variance (ANOVAs) revealed significant group differences with respect to all of these measures. More specifically, the healthy controls, BPD participants, and participants with dysthymia differed with respect to scores on the BDI ($F_{2,30} = 17.42$, $P < .001$), PANAS trait positive mood ($F_{2,31} = 14.57$, $P < .001$), PANAS trait negative mood ($F_{2,31} = 24.13$, $P < .001$), MASQ anhedonia ($F_{2,31} = 27.91$, $P < .001$), and MASQ anxious arousal ($F_{2,31} = 8.78$, $P = .001$).

Table 1 shows the mean scores for these measures. Post hoc Tukey honestly significant differences tests revealed that participants with BPD and dysthymia reported higher levels of depression on the BDI, more anhedonia on the MASQ, and were characterized by less trait-like positive mood on the PANAS than were the healthy controls. Participants with BPD also reported more trait negative mood and more anxious arousal on the MASQ than did the controls. However, for both of these measures, the differences between the participants with dysthymia and the controls or between the participants with dysthymia and those with BPD did not reach statistical significance.

In addition, participants with BPD reported higher levels of anxious arousal on the MASQ than did the participants with dysthymia. The BPD group also had higher levels of PANAS trait negative mood (but not trait positive mood) than the dysthymia group.

Evaluation of EOI Comments

After scanning was completed, participants were shown the 4 EOI comments that they had heard during the functional imaging and asked to rate the valence, arousal, and self-relevance for each one. Group means (for all 4 comments combined) are shown in Table 1. All participants rated the EOI comments in the negative range of the scale, and there were no between-group differences with respect to how negative the EOI comments were rated as being ($F_{2,30} = 1.39$, NS). There was also no significant between-groups difference in how emotionally arousing participants felt the EOI comments were ($F_{2,30} = 2.91$, $P = .07$). However, ratings of the self-relevance of the EOI comments did differ across the groups ($F_{2,31} = 17.56$, $P < .001$), with the BPD and dysthymia participants rating the EOI comments as being more likely to have been said about them than the controls did. Participants in the BPD group were especially likely to personalize the comments, rating them as significantly more personally relevant than they were rated by the participants with dysthymia.

Table 1. Clinical Characteristics of Borderline Personality Disorder (BPD), Dysthymia, and Control Participants[a,b]

Measure	Control	Dysthymia	BPD
BDI	1.0 (1.48)†	13.4 (7.44)†	21.00 (11.60)†
PANAS			
Trait negative mood	16.09 (5.24)†	19.10 (6.95)‡	31.31 (5.00)†‡
Trait positive mood	35.27 (8.37)†	20.30 (3.88)†	23.35 (7.11)†
MASQ			
Anhedonia	10.91 (3.05)†	20.90 (5.34)†	25.69 (5.69)†
Anxious arousal	19.32 (2.76)†	25.43 (10.08)‡	32.85 (12.17)†‡
EOI comments			
Valence	6.59 (1.23)	5.60 (1.49)	5.77 (1.67)
Arousal	4.89 (2.42)	6.10 (1.08)	6.75 (1.79)
Self-relevance	1.91 (1.15)†	3.93 (1.73)†‡	6.19 (2.1)†‡
Negative mood change after EOI	1.1 (3.31)	2.10 (2.08)	2.62 (6.84)
Positive mood change after EOI	−1.90 (2.96)	−0.90 (2.33)	−2.15 (4.12)

[a]Figures are expressed as means. Standard deviations are in parentheses.
[b]Mean values with the same dagger/double dagger symbols are significantly different from each other at $P < .05$.
Abbreviations: BDI = Beck Depression Inventory, EOI = emotional overinvolvement, MASQ = Mood and Anxiety Symptom Questionnaire, PANAS = Positive and Negative Affect Schedule.

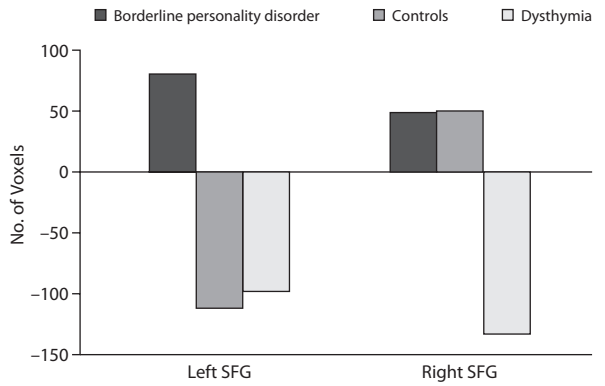
Mood Changes After Hearing EOI

Participants provided mood ratings at regular intervals while they were in the scanner. To provide a measure of mood change after exposure to EOI, PANAS mood ratings collected immediately after the EOI stimulus block were subtracted from PANAS mood ratings obtained immediately prior to EOI exposure. One-way ANOVAs revealed no group differences in mood change in response to the EOI comments. This was true both for positive mood, ($F_{2,30} = 0.28$, NS) and also for negative mood, ($F_{2,30} = 0.99$, NS). In other words, compared to the healthy controls and the participants with dysthymia, participants with BPD were not more emotionally reactive to the EOI stimuli, at least as reflected in their self-reported mood changes. Paired *t* tests revealed that all participants reported significantly more negative mood after hearing the EOI comments than they did before (mean = 14.51 versus 16.51, $t_{32} = 2.47$, $P = .021$). They also reported a significant decline in positive mood (mean = 26.97 versus 24.82, $t_{32} = -3.00$, $P = .005$).

Evaluation of Neutral Comments

PANAS mood ratings obtained after the block of 4 neutral comments revealed that exposure to neutral comments did not change participants' positive or negative moods in any significant way. Before hearing the neutral comments, the mean positive mood of participants was 25.78; after the comments it was 25.76 ($t_{32} = 0.05$, NS). For negative mood

Figure 1: Activation in Left and Right Superior Frontal Gyrus (SFG) During Presentation of Emotional Overinvolvement Comments[a]



[a]Activation in left SFG is significantly greater in participants with borderline personality disorder compared to the other 2 groups ($t_{31} = 2.31$, $P = .028$, 2-tailed).

the means were 15.58 before and 15.00 after hearing the neutral comments, ($t_{32} = -1.01$, NS). One-way ANOVAs revealed no significant main effect of diagnostic group for either positive or negative mood change after hearing the neutral comments ($F_{2,30} = 0.46$, NS, for positive mood and $F_{2,30} = 0.39$, NS, for negative mood). Finally, when participants were asked to rate the valence of the neutral comments using a 1–9 scale (1 = very positive; 9 = very negative), all groups rated the neutral comments in the middle range of the scale (4.88 for BPD participants, 4.63 for dysthymia participants, and 4.36 for controls) and there were no differences in valence ratings across the 3 study groups. In other words, the data suggested that participants experienced the neutral comments as neutral. There was also no evidence to suggest that participants in any one group showed a different reaction to the neutral comments than participants in any other group.

Activation Changes During EOI

Prefrontal areas. For each subject, activation to the neutral (comparison) condition was subtracted from activation to the EOI condition. Using a random-effects paired *t* test analysis, we made direct comparisons between the EOI minus neutral contrast for each diagnostic group. Using the region of interest method described earlier, the number of voxels above threshold was extracted for each individual. This voxel count was then used to test for differences in group × hemisphere responses.

The primary hypothesis that during EOI participants with BPD would show greater activation of left prefrontal areas than healthy controls or participants with dysthymia was supported by the data. A 3 (group) × 2 (left and right hemisphere) repeated-measures ANOVA revealed no main effect for hemisphere across the 3 study groups ($F_{1,31} = 0.88$, NS). However, there was a significant group-by-hemisphere interaction ($F_{2,31} = 3.61$, $P = .039$, partial $\eta^2 = .19$). As shown in Figure 1, during EOI, participants with BPD showed a mean *increase* (79.5) in the number of voxels activated in left superior frontal gyrus (SFG), a more defined prefrontal region. In contrast, both healthy controls and participants with dysthymia showed a mean *decrease* (–112.3 and –98.6, respectively) in activation in left SFG during EOI. Further examination of the data revealed that 9/13 (69%) of participants with BPD showed the predicted increase in left prefrontal activation during EOI. However, this pattern was found in only 3/11 (27%) of the controls and in 3/10 (30%) of the dysthymia participants. There were no differences between the 3 study groups for activation in right SFG during EOI.

Amygdala. As hypothesized, there were no differences between the BPD subjects and the controls with respect to amygdala activation during exposure to EOI. During EOI, the mean number of voxels activated bilaterally in amygdala by the BPD participants was 6.08. For the controls the number was 15.09 ($t_{22} = -.051$, NS). In other words, participants with BPD processed EOI statements in a manner that was comparable to controls (Figure 2).

This was not the case for the participants with dysthymia, however. During exposure to EOI, participants with dysthymia showed significantly increased bilateral amygdala activity relative to participants with BPD (mean = 53.40 versus 6.08, $t_{21} = 2.37$, $P = .027$; see Figure 2). Participants with dysthymia also showed increased amygdala activation during EOI relative to controls (mean = 53.4 vs 15.09, $t_{19} = 2.28$, $P = .034$). Taken together, these findings suggest that, at the level of the amygdala, the BPD participants were much less reactive to EOI than were the participants with dysthymia, producing amygdala activation that was comparable to that found in the healthy controls.

Clinical Correlates of Increased Left Prefrontal Activation to EOI

In an exploratory set of analyses, we examined the extent to which scores on the clinical self-report measures were correlated with increased left prefrontal activation during exposure to EOI comments. We also explored the correlation between increased left prefrontal activation and several subscales of the SNAP (which was completed at time of entry into the study). To reduce the number of correlations and so limit the potential for type 1 error, we excluded 8 SNAP subscales that were less relevant to the clinical construct of BPD (eg, workaholism).

As is apparent from Table 2, increased left prefrontal activation during EOI was associated with higher BDI scores on the day of the scan and higher scores on the anhedonic depression subscale of the MASQ. Of the 7 SNAP subscales examined, 5 were significantly correlated with left prefrontal activation to EOI. These included higher scores on negative temperament, mistrust, manipulativeness, self-harm, and eccentric perceptions. What is most striking about these findings is that these characteristics are central to the clinical construct of BPD. These supplementary analyses therefore support the idea that increased

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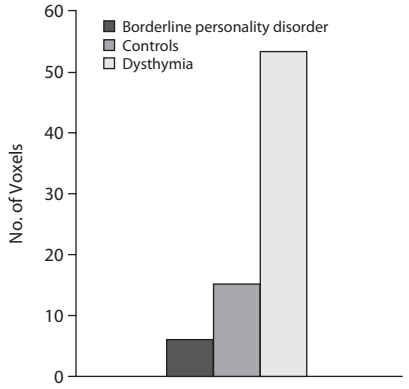
Figure 2: Activation in Amygdala During Emotional Overinvolvement[a]



[a]Activation in participants with dysthymia is significantly greater than activation in controls ($P = .034$) or participants with borderline personality disorder ($P = .027$).

Table 2. Clinical Correlates of Increased Left Prefrontal Activation to EOI

Clinical Measure	r[a]	P
BDI	0.45	.008
MASQ		
Anhedonia	0.43	.001
Anxious arousal	0.34	.052
PANAS		
Trait negative mood	0.34	.052
Trait positive mood	0.00	NS
SNAP		
Negative temperament	0.39	.021
Mistrust	0.35	.042
Manipulativeness	0.42	.015
Self-harm	0.41	.015
Eccentric perceptions	0.54	.001
Impulsivity	0.32	.063
Aggression	0.18	NS

[a]All correlations are 2-tailed.
Abbreviations: BDI = Beck Depression Inventory, EOI = emotional overinvolvement, MASQ = Mood and Anxiety Symptom Questionnaire, NS = not significant, PANAS = Positive and Negative Affect Schedule, SNAP = Schedule for Nonadaptive and Adaptive Personality.

left prefrontal activation to EOI may reflect something particularly relevant to BPD.

DISCUSSION

This is the first study to explore the link between EOI and better clinical outcomes in patients with BPD through an examination of the neural correlates of EOI. As hypothesized, when activation to neutral comments was subtracted from activation to EOI, participants with BPD demonstrated increased left prefrontal activity during EOI relative to both healthy controls and participants with dysthymia. To the extent that left prefrontal activation (as indexed by SFG) is associated with the processing of approach-related stimuli,[18] these findings support the hypothesis that EOI is an especially engaging and possibly positive stimulus for those with BPD.

Importantly, amygdala activation in people with BPD during EOI was comparable to that found in the healthy controls. This is especially interesting because morphometric studies have found evidence of altered amygdala volumes in BPD relative to psychiatrically healthy comparison groups.[6,36,37] Also worthy of mention is that the BPD participants did not show greater amygdala activation during EOI than the participants with dysthymia did, even though hyperarousal to negative stimuli has been reported in prior research.[7,8]

In contrast to the BPD group, it was the participants with dysthymia who responded to EOI with increased amygdala activation. This finding is especially interesting because EOI is part of the expressed emotion index and because high levels of expressed emotion are known to predict relapse in depression.[1,24] In other work, we have demonstrated that people vulnerable to depression respond to criticism (another element of the expressed emotion index) with increased amygdala activation.[12] The finding that participants with dysthymia respond to EOI with increased amygdala activation is consistent with the idea that there is something about expressed emotion that is capable of perturbing nodes in the neural circuitry that underlies depressive illness. This may be important for understanding the expressed emotion–relapse link. For people with BPD, EOI is associated with a favorable clinical outcome.[3] One implication of the current findings is that the absence of amygdala hyperreactivity to EOI as well as the presence of increased reactivity in SFG in those diagnosed with BPD may be positive prognostic signs.

Although hearing EOI comments activated left prefrontal areas in the BPD participants, their self-report data provided no indication that they experienced EOI in a positive way. Like the controls and the participants with dysthymia, those with BPD rated EOI as a negatively valenced stimulus. The BPD group also responded to EOI with an increase in self-reported negative mood and a decrease in positive mood on the PANAS. The inconsistency between the brain-activation patterns associated with hearing EOI and patients' self-reports warrants some explanation.

It is possible that our BPD participants were simply unwilling to report positive mood changes that resulted from hearing EOI comments because of concerns about social desirability. However, there was no indication that this was the case. These observations therefore raise the possibility that one problem associated with BPD may be an inability to become consciously aware of approach-related positive neural experiences. Cognitive studies have suggested that BPD may be associated with negative processing biases.[38,39] Although speculative, it is plausible to suggest that BPD may be associated with an internal bias with regard to the neural experiences that are allowed to enter into awareness. If the system is biased toward bringing negative neural experiences into awareness, it may be more difficult for neural experiences associated with positivity or reward

to enter a system of processing that would permit them to be experienced in a manner that would make them amenable to self-report. Such an idea is consistent with the high levels of negative affectivity reported in people with BPD. It might also help explain why chronic negative affectivity remains so much a part of the disorder,[15] even in the face of clinical improvement in other areas.

Another interpretation of our findings, however, is that increased left prefrontal activation in the BPD participants is indicative of greater effortful control in response to EOI. Although this is a plausible explanation, the data in Figure 1 do not seem fully consistent with this idea. If left prefrontal activation reflects efforts to regulate responses to the EOI stimuli, why do the participants with dysthymia (who also have clinical pathology) show comparable levels of left prefrontal activation to the controls? Moreover, for right prefrontal activation, activation to EOI is similar in both BPD participants and controls. Taken together, these findings suggest that differences in effortful control may not provide a satisfactory explanation of our data. However, it remains possible that other functions associated with left SFG, including working memory,[40] might be relevant for understanding our findings.

In this study, we constrained our analyses to a limited number of regions of interest (prefrontal cortex and amygdala) that were important for the specific hypothesis that we wanted to test (ie, that people with BPD would process EOI as if it were an approach-related stimulus). This has the advantage of reducing the potential for type 1 error. However, other brain areas that we did not examine may also be important and should be considered in future investigations of this type. Such areas include those known to be involved in reward processing, such as the nucleus accumbens, caudate, putamen, and globus pallidus.[41]

Our study is also limited by small sample sizes and the focus only on females. Although the majority of BPD research involves female or predominantly female samples, BPD also occurs in males.[42,43] In future work, it will be important to learn if the findings reported here can be generalized to males with the disorder. It will also be important to learn how unequivocally positive or negative auditory challenges (that do not involve EOI) are processed by those with BPD. Such work would allow us to understand more about the extent to which the present findings are specific to EOI.

The differences in the patterns of responses to EOI in participants with BPD versus those with dysthymia are especially interesting given the high levels of comorbidity between BPD and mood disorders, both generally and in our sample. Many of our BPD participants were currently dysthymic or were suffering from depression. In addition, many of our currently dysthymic participants had past histories of major depression. Use of antidepressant medications was also high in both groups. The overlap between the groups with regard to vulnerability to mood disorders and exposure to antidepressant medications might have led us to expect generally similar patterns of activation in response to EOI. However, the distinct pattern of findings suggests that there may be something quite different about BPD and that BPD may be a form of psychopathology that is distinct from mood disorders. These findings have implications for the conceptual understanding of BPD and its links to affective illness.[44–47]

Our findings may also have treatment implications. High family levels of EOI have been linked to better clinical outcomes in BPD,[3] suggesting that there may be something about EOI that activates approach-related neural circuitry for patients with this disorder. The increased left prefrontal activation that is found in people with BPD when they are exposed to EOI comments is consistent with this. Of course, in the absence of follow-up data showing that patients who show increased left prefrontal activation to EOI have a more favorable clinical course, strong conclusions about the implications of these data are not warranted. Nonetheless, the results of this exploratory study are quite provocative. Our findings show that EOI is not a stimulus that people with BPD report liking. Those with the disorder may therefore not respond well when family members express the kinds of worries and concerns that may actually be beneficial for BPD sufferers to hear. At the very least, based on our data, it would seem that clinicians should not try to reduce naturally occurring high EOI attitudes in the relatives of BPD patients when they are present. To the extent that EOI is associated with increased levels of amygdala activation in people with dysthymia and is associated with relapse in depression, the presence of EOI in the families of patients with mood disorders may be a greater source of clinical concern.

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