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# Amygdala Hyperreactivity in Borderline Personality Disorder: Implications for Emotional Dysregulation

Nelson H. Donegan, Charles A. Sanislow, Hilary P. Blumberg, Robert K. Fulbright, Cheryl Lacadie, Pawel Skudlarski, John C. Gore, Ingrid R. Olson, Thomas H. McGlashan, and Bruce E. Wexler

**Background:** *Disturbed interpersonal relations and emotional dysregulation are fundamental aspects of borderline personality disorder (BPD). The amygdala plays important roles in modulating vigilance and generating negative emotional states and is often abnormally reactive in disorders of mood and emotion. The aim of this study was to assess amygdala reactivity in BPD patients relative to normal control subjects. We hypothesized that amygdala hyperreactivity contributes to hypervigilance, emotional dysregulation, and disturbed interpersonal relations in BPD.*

**Methods:** *Using functional magnetic resonance imaging, we examined neural responses to 20-sec blocks of neutral, happy, sad, and fearful facial expression (or a fixation point) in 15 BPD and 15 normal control subjects. The DSM IV-diagnosed BPD patients and the normal control subjects were assessed by a clinical research team in a medical school psychiatry department.*

**Results:** *Borderline patients showed significantly greater left amygdala activation to the facial expressions of emotion (vs. a fixation point) compared with normal control subjects. Post-scan debriefing revealed that some borderline patients had difficulty disambiguating neutral faces or found them threatening.*

**Conclusions:** *Pictures of human emotional expressions elicit robust differences in amygdala activation levels in borderline patients, compared with normal control subjects, and can be used as probes to study the neuropathophysiologic basis of borderline personality disorder.* Biol Psychiatry 2003;54:1284–1293 © 2003 Society of Biological Psychiatry

## Introduction

A core problem of borderline personality disorder (BPD) is emotional dysregulation (Clarkin et al 1993; Sanislow et al 2000), which results from a combination of emotional vulnerability and an inability to modulate emotional responses (Gunderson and Zanarini 1989; Linehan 1993, 1995). Emotional vulnerability is characterized by a marked sensitivity to emotional stimuli (low threshold) and unusually strong reactions (high amplitude) that are abnormally slow in returning to baseline (long duration). According to Linehan (1995), "... most of the problems exhibited by borderline individuals are either the direct or indirect consequence of emotion dysregulation or attempts to modulate intense emotional reactions." From this perspective, many of the erratic self-destructive, impulsive, or self-injurious behaviors that are part of the constellation of symptoms of BPD might be understood as products of emotional dysregulation. Most often (and most dramatically), these are manifest in the context of a pattern of unstable and intense interpersonal relationships (DSM-IV, criterion 2, p. 654 [American Psychiatric Association 1994]; also see Benjamin 1993 and Linehan 1993).

Findings from a diverse range of animal and human experiments indicate that the amygdala is an element of brain systems involved in the generation of negative emotional states (Amaral 2002; Davis 2000; Emery et al 2001; LeDoux 2000; Meunier et al 1999). It is often hyperactive in mood and emotional disorders, such as posttraumatic stress disorder (PTSD) (Rauch et al 2000), depression (Drevets 1998), and generalized anxiety disorder (Johnstone et al, unpublished data; Thomas et al 2001). Humans with selective bilateral damage to the amygdala show impaired fear conditioning (Bechara et al 1995), a failure to show enhanced perception of stimuli with aversive content (Anderson and Phelps 2001), and impairments in making negative evaluations of human faces that have been rated untrustworthy and unapproachable by normal subjects (Adolphs et al 1998). In social situations, the amygdala is thought to play an important role in modulating attention/vigilance (especially in evaluating

potentially threatening social situations), the valence of events/objects, and perceiving the emotional expressions of others (Amaral 2002; Rolls 1999; Whalen 1998). For these reasons, we take the amygdala as a starting point for developing a brain-system-level model of vigilance and negative emotional states and for identifying abnormalities within these systems that are responsible for emotional dysregulation.

Research on BPD in which imaging technologies are used to assess amygdala function is limited. Positron emission tomography studies have found hypometabolism in prefrontal cortex (PFC) of BPD patients compared with normal control (NC) subjects (De la Fuente et al 1997; Soloff et al 2000) and above-normal activation of dorsolateral PFC and anterior PFC when BPD patients were presented with scripts designed to evoke memories of abandonment (Schmahl et al 2003). In a magnetic resonance spectroscopy study, Tebartz van Elst et al (2001) observed decreased levels of N-acetyl aspartate (suggestive of impaired neural functioning) in BPD patients compared with NC subjects in the dorsolateral PFC. Structural magnetic resonance imaging (MRI) studies have found smaller frontal lobe volume in BPD patients (Lyoo et al 1998) and reduced hippocampal and amygdala volume (Dreissen et al 2000). In the one functional MRI (fMRI) study that we are aware of, Herpertz et al (2001) reported greater amygdala activation in six BPD patients without co-occurring Axis 1 disorders, compared with NC subjects, when they viewed aversive slides (e.g., mutilated bodies) relative to neutral slides (e.g., household objects).

To assess amygdala reactivity in BPD subjects, we selected pictures of human facial expressions of emotion (Ekman and Friesen 1979) that have been shown in imaging studies to activate the amygdala in NC subjects and elicit abnormal levels of activity in individuals with mood and anxiety disorders. For example, a number of laboratories have demonstrated that fearful faces activate the amygdala in NC subjects (Breiter et al 1996; Morris et al 1996; Vuilleumier et al 2001; Whalen et al 1998), as well as in individuals with anxiety disorders (Thomas et al 2001) and PTSD (Rauch et al 2000; however there was no assessment for Axis II disorders). We predicted that differences in amygdala activation between the BPD and NC groups would be greatest to faces with negative emotional valences.

## Methods and Materials

### Subjects

Subjects were recruited by advertisements placed in the community and on treatment units at affiliated clinical sites. The NC group comprised 15 right-handed subjects, nine (60%) of whom were female; the BPD group comprised 15 right-handed subjects,

13 (86%) of whom were female [$\chi^2(3) = 1.5$, $p = .107$]. Mean (SD) age was 35.0 (11.7) years for the BPD group and 34.9 (10) for the NC group [$F(1,28) = .001$, $p = .99$]; see Table 1. All subjects included in the BPD group were currently in psychiatric treatment or had been in treatment within the past 6 months. Subjects were prescreened and excluded for organic mental impairment, the presence of schizophrenia spectrum disorders, and substance intoxication. Subjects were also excluded if unable to refrain from abusing substances for a 2-week period before the experiment (by self-report), or were unable to undergo MRI scanning. One subject was excluded from the NC group owing to computer malfunction during fMRI. Five subjects were excluded from the BPD group (one owing to weight/excessive girth, three for movement during fMRI, and one owing to computer malfunction). Informed consent was obtained in all cases. The procedures were reviewed and approved by the Human Investigation Committee of the Yale University School of Medicine.

### Assessment

Subjects underwent a comprehensive diagnostic assessment. Treatment histories and psychosocial functioning were assessed with the Longitudinal Interval Follow-up Evaluation–Baseline (Keller et al 1987). The Structured Clinical Interview for DSM-IV Axis I Disorders–Patient Version (SCID-I/P; First et al 1996) was used to assess Axis I disorders and the Diagnostic Interview for Personality Disorders-IV (DIPD-IV; Zanarini et al 1996) for Axis II disorders. The DIPD-IV has been demonstrated to be reliable (Zanarini et al 2000). Raters were postdoctoral clinical psychologists trained to reliable standards on Axis I and II; their performance was monitored throughout the study by the rating and reviewing of videotapes on a monthly basis.

Subjects in the BPD group ($n = 15$) were required to meet full criteria (five of nine) for BPD on the DIPD-IV. On average, these subjects additionally met criteria for 1.1 other Axis II personality disorders (SD = 1.4, range 0–4; see Table 1). For Axis I, the most prominently co-occurring disorders included major depressive disorders (MDDs), PTSD, and substance use disorders (see Table 1). Eleven of the 15 BPD patients were taking psychotropic medications (see Table 1), and 4 were medication free (three had never taken psychotropic medications and one had stopped taking fluvoxamine 2.9 years before the scan).

For the NC group ($n = 15$), stringent guidelines were used for inclusion to minimize the presence of Axis I and II pathology. These subjects had to demonstrate fewer than 10 DIDP-IV criteria overall, no personality disorder "features" on any one personality disorder (e.g., at least two fewer than required for the diagnosis), no BPD criteria on the DIPD-IV, no Axis I psychopathology by SCID-I/P, no psychotropic medication, and no psychiatric treatment.

### Stimulus Presentation

Functional MRI sessions consisted of eight runs, each lasting 4 min 20 sec. Runs were subdivided into 20-sec epochs or blocks; 20 pictures of a particular facial expression or a fixation point were presented at a rate of 1/sec during each block. Facial expressions of fear, sadness, happiness, or neutral expressions

Table 1. Medications, DSM-IV Axis I Diagnoses, and Axis II Diagnoses (other than BPD) for Patients in the BPD Study Group

| Patient No. | Gender | Age (years) | Medications | Axis I Diagnoses | Additional Axis II Diagnoses |
|---|---|---|---|---|---|
| 1 | F | 51 | 1, 2, 5 | MDD, BULIMIA; h/o ETOH | AVPD; DPD features |
| 2 | M | 33 | 1, 3 | PTSD, DYS, ED NOS; h/o ETOH | AVPD, DPD, PPD, NPD; ASPD features |
| 3 | F | 50 | 3, 4 | PTSD, BIPOL I, SOCPHOB, ETOH, SUD | AVPD, OCPD, ASPD; DPD, NPD, STPD features |
| 4 | F | 29 | 3, 5, 7 | BIPOL I; h/o, ETOH, SUD | DPD, OCPD, ASPD; HPD features |
| 5 | F | 31 | None | MDD, GAD, SOCPHOB, OCD, ED NOS, ETOH; h/o PTSD | None; AVPD, OCPD features |
| 6 | F | 37 | 1, 2 | PTSD, DEP NOS, ANX NOS; h/o ETOH, SUD | AVPD, ASPD; OCPD features |
| 7 | F | 24 | None | MDD, DYS, ANX NOS | None; AVPD, OCPD features |
| 8 | F | 32 | 1, 3, 4 | PTSD, MDD, SOCPHOB, BULIMIA; h/o ED NOS, GAD, ETOH, SUD | AVPD; OCPD, DPD features |
| 9 | F | 46 | 2, 5, 6 | PTSD, MDD | None |
| 10 | F | 43 | 1, 2, 3, 4, 5 | PTSD, BIPOL I, ED NOS; h/o SUD, ETOH | None |
| 11 | F | 34 | 1, 3, 4, 5, 8 | PTSD, BIPOL I, OCD, PD, ED NOS, ETOH, SUD | None; AVPD features |
| 12 | F | 55 | 1, 4 | MDD, PD, ETOH; h/o SUD | None |
| 13 | F | 20 | None | GAD, ED NOS | AVPD, OCPD |
| 14 | M | 22 | None | MDD; h/o ETOH, SUD | None |
| 15 | F | 19 | 1, 3, 4 | h/o MDD, ETOH | None; NPD features |

Medications: 1, selective serotonin reuptake inhibitor; 2, tricyclics; 3, anticonvulsants; 4, benzodiazepine; 5, antipsychotic; 6, anticholinergic; 7, methadone; 8, ritalin. Axis I disorders: MDD, major depressive disorder; BULIMIA, bulimia nervosa; ETOH, alcohol abuse; PTSD, posttraumatic stress disorder; DYS, dysthymic disorder; ED NOS, eating disorder not otherwise specified; BIPOL I, bipolar I disorder; SOCPHOB, social phobia; SUD, substance abuse disorder (other than alcohol); GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; DEP NOS, depressive disorder not otherwise specified; ANX NOS, anxiety disorder not otherwise specified; PD, panic disorder. Axis II disorders: AVPD, avoidant personality disorder; DPD, dependent personality disorder; PPD, paranoid personality disorder; NPD, narcissistic personality disorder; ASPD, antisocial personality disorder; OCPD, obsessive-compulsive personality disorder; STPD, schizotypal personality disorder; HPD, histrionic personality disorder. Note: "Features" is defined as one criterion fewer than required for the personality disorder. BPD, borderline personality disorder; F, female; M, male; h/o, history of.

were chosen from the Ekman and Friesen series (see Figure 1). Photographs of five women and five men, with each individual exhibiting each of the four expressions, comprised the stimulus set of 40 pictures.

Each of the happy, sad, and fearful blocks of faces occurred twice in each run. Each one of these blocks was preceded by a block of neutral faces and followed by a block with the fixation point (on half of the runs) or preceded by fixation point and followed by a neutral block (on the remaining half of the runs). Ordering of the emotional expressions within runs was systematically varied across the session to control for sequential dependencies. Within each 20-sec block of faces, pictures of the 10 individuals were presented twice, with the ordering of individuals being constrained by one of three counterbalanced gender transition sequences assigned to a particular block. Otherwise, the ordering of the individual pictures was randomized across the blocks.

Images were back-projected onto a screen and viewed by subjects through an angled mirror fixed above their face during the imaging procedure. Stimulus presentations and timing were computer-controlled by Psyscope software (Cohen et al 1993). The subjects had no other task than to attend to the faces. No task was imposed to create a situation with minimal structure.

## fMRI Acquisition

Images were acquired on a GE Signa 1.5-Tesla LX imager (General Electric, Milwaukee, WI) equipped with fast gradients and a standard quadrature head coil. Subjects lay supine in the magnet with their heads immobilized by a neck support, foam wedges, and a restraining band drawn around the forehead. Scout images in the sagittal plane were obtained with parameters of echo time (TE) = 14 msec, repetition time (TR) = 500 msec, field of view = 24 × 24 cm, slice thickness = 5 mm, no gap, 20



Figure 1. Examples of neutral, happy, sad, and fearful facial expressions from the Ekman and Friesen (1979) series.

slices, and a data matrix of 256 × 192. Sixteen anatomic images were acquired in a coronal–oblique plane perpendicular to the anterior and posterior commissures, with parameters of TR = 500 msec, TE = 14 msec, field of view = 20 × 20 cm, an imaging matrix of 256 × 256, and 7-mm-thick slices. These images extended from the PFC to the occipitotemporal region. In each subject, the eighth slice of the coronal images was centered on the amygdala by visual inspection to include the amygdala and by use of the reference landmarks of the pituitary stalk, posterior pituitary, and dorsal sella (Bronen and Cheung 1991). During the presentation of the facial stimuli in each 20-sec block, 12 functional images were collected at each of the same sixteen locations with a single shot, echo-planar gradient echo sequence with parameters of TR = 1650 msec, TE = 60 msec, flip angle = 60°, field of view = 20 × 20 cm, and a 64 × 64 data matrix, providing a 3.1 × 3.1-mm in-plane resolution.

### fMRI Data Analysis

Before statistical analysis, the images from each run were motion-corrected for three translation directions and for the three possible rotations (Friston et al 1995). Subjects were required to meet two motion criteria: translational displacement less than 1.5 mm and rotational displacement less than 2°. Two images at each slice location at the beginning of a run were discarded, as was one image at each slice location at the beginning of each subsequent block in the run, to account for signal intensity variation that occurred at the beginning of an echo-planar sequence and from the hemodynamic changes in response to a task transition. The remaining images were spatially filtered with a Gaussian filter with a full-width half-maximum value of 6.25 mm. Activation maps were created that compared a subject's response to each of the four facial expressions to its own fixation-point baseline. (Differences in activation levels between particular facial expressions with the fixation-point baseline blocks were determined by comparing the designated blocks within each individual run.) Both the signal change maps and the anatomic images from individual subjects were transformed by in-plane transformation and slice interpolation into a normalized three-dimensional grid, defined by Talairach and Tournoux (1988).

Activation maps from individual subjects were used as a derived measure of task-related activity and were combined by averaging across subjects to obtain group composite signal change maps. To avoid the need to assume a specific distribution and variance of the data, a randomization procedure was used to estimate $p$ values of the group composite maps (Hays 1988; Manly 1997; Nichols and Holmes 2001). To randomize, the sign of the activation measure for each voxel (mean percent signal change) was reversed in randomly generated subsets of subjects. The activation measure was then recalculated. This procedure was repeated 10,000 times, thereby generating a distribution of the activation measures. The proportion of times that the observed activation measure was more extreme than a randomized value represents a $p$ value, or the proportion of times a mean activation as large or larger than the one obtained would be expected if the null hypothesis (no difference between tasks) were true. The $p$ value for each voxel was overlaid on the mean
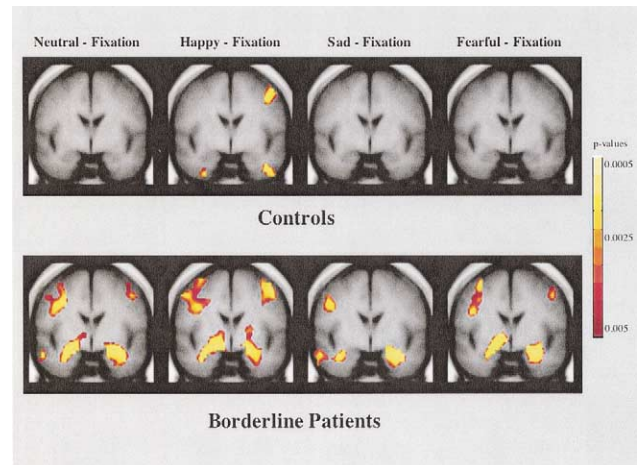


Figure 2. Activation map showing regions in the amygdala slice in which activation exceeded the criterion threshold level of $p <$ .005 for the normal control and borderline personality disorder groups for each of the four facial expressions.

anatomic image (a group composite of the T1-weighted images) for display, with a threshold of $p <$ .005.

### Region of Interest: The Amygdala

The amygdala region of interest (ROI) was defined in each hemisphere according to gyral and sulcal landmarks to select the rectangular volumes of Talairach space (half-size of unit Talairach volume). The rectangular volumes were large enough to account for anatomic variability among subjects and to ensure coverage of the amygdala in all subjects. The Talairach coordinates of the amygdala ROIs were centered on x = +/−23, y = −4, and z = −4, and the region size for each hemisphere was 50 voxels. Activation levels were calculated as the sum of the percent-positive-signal-change for all individual voxels in the region that survived thresholding and cluster filtering procedures ($p$ = .05, cluster size = 15).

### Statistical Analysis

Results of the ROI analyses were evaluated with a three-way repeated-measures analysis of variance (ANOVA), in which the between-groups factor was diagnosis (BPD vs. NC) and the within-group factors were hemisphere (right vs. left amygdala) and facial expression (neutral, happy, sad, fearful). Paired comparisons were conducted with one-way ANOVAs.

## Results

### Right and Left Amygdala Activation

Borderline personality disorder patients exhibited high levels of left amygdala activation to the facial expressions (relative to the fixation point; Figure 2). Other areas that
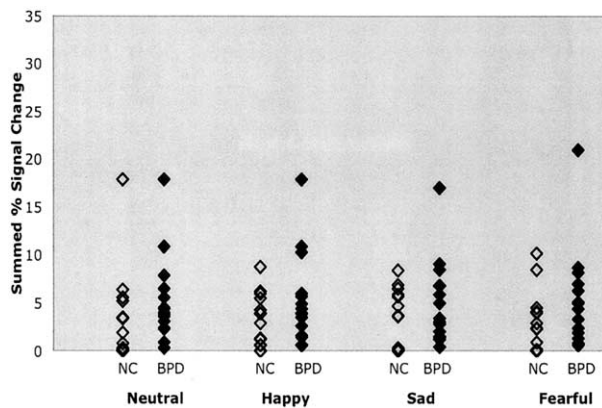
Figure 3. Right amygdala activation levels for individual subjects within the normal control (NC) and borderline personality disorder (BPD) groups to each of the four facial expressions.
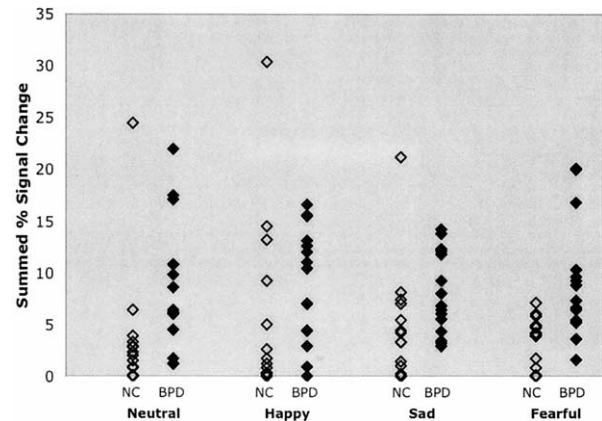


Figure 4. Left amygdala activation levels for individual subjects within the normal control (NC) and borderline personality disorder (BPD) groups to each of the four facial expressions.

showed suprathreshold activation in Figure 2 include regions containing the dorsal border of the amygdala, the bed nucleus of the stria terminalis, the lateral hypothalamic nuclei, the nucleus basalis, and regions in the frontal lobes. For the NC subjects, the facial expressions activated the left amygdala relative to the fixation point baseline (see above), but the activation levels did not exceed the strict criterion activation-threshold used in Figure 2 ($p < .005$).

The results of amygdala ROI analyses are presented in Figure 3 (right amygdala) and Figure 4 (left amygdala), which show activation levels to each of the four facial expressions (vs. fixation point) for each subject. In the left amygdala, the least amount of overlap between the groups was observed with the neutral facial expressions and the greatest amount with the happy expressions.

A three-way ANOVA, for which the factors were diagnosis $\times$ hemisphere $\times$ facial expression, showed a significant main effect of group [$F(1,28) = 7.57, p = .01$] and a significant main effect of hemisphere [$F(1,28) = 8.37, p < .01$]. No other main effects or interactions reached conventional levels of significance. Planned comparisons of the BPD and NC groups' activation levels to the four facial expressions revealed that BPD patients showed reliably greater levels of left amygdala activation compared with NC subjects to the neutral faces [$F(1, 28) = 5.24, p < .05$], the sad faces [$F(1,28) = 4.14, p = .05$], and the fearful faces [$F(1,28) = 12.53, p < .001$] but not the happy faces [$F(1,28) = 1.88, p > .15$]. Comparisons of right amygdala activation revealed no significant group differences ($p > .10$ in all cases). As can be seen in Figure 4, there was an outlier in the control group; the left amygdala activation levels of this subject to the neutral, happy, and sad facial expressions were even greater than any subject's in the BPD group. Running the ANOVA

without the outlier in the control group resulted in a significant main effect of group [$F(1,27) = 13.37, p < .001$] and hemisphere [$F(1,27) = 7.37, p < .01$] and a significant group $\times$ hemisphere interaction [$F(1,27) = 5.54, p < .05$]. Planned comparisons showed that BPD patients showed reliably greater levels of left amygdala activation compared with NC subjects to the neutral [$F(1,27) = 15.20, p < .001$], happy [$F(1,27) = 7.48, p = .01$], sad [$F(1,27) = 13.15, p = .001$], and fearful faces [$F(1,27) = 10.94, p < .005$]. Comparisons of right amygdala activation revealed no significant group differences (Figure 5).
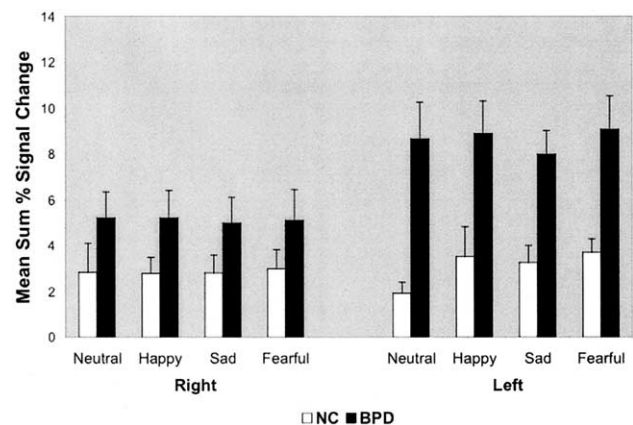


Figure 5. Mean levels of right and left amygdala activation in the borderline personality disorder (BPD) and normal control (NC) (without the outlier) groups to the four facial expressions. Error bars show the SEM.

## Post Hoc Comparisons

**GENDER.** There were 13 female and two male subjects in the BPD group and nine female and six male subjects in the NC group. The greater number of men in the NC group did not augment the overall differences in left amygdala activation between the NC and BPD groups; in the NC group, the mean (SEM) levels of left amygdala activation (as defined above) for women ($n = 9$) to the neutral, happy, sad, and fearful expressions were 3.8 (2.6), 5.4 (3.5), 4.1 (2.2), and 3.1 (.85), respectively; for the men ($n = 6$), 2.8 (.92), 5.2 (2.1), 5 (1.3), and 4.1 (.86), respectively.

**PSYCHOTROPIC MEDICATION.** Because psychotropic medications can potentially affect amygdala reactivity and thereby complicate interpretations of group differences, we more closely examined BPD subjects by their medication status. Four of the 11 BPD patients were not on medication. Examining left amygdala activation (as defined above) to the neutral, happy, sad, and fearful expressions, the means (SEM) for the no-medication group ($n = 4$) were 8.5 (3.2), 12.3 (2.8), 5.7 (.9), and 9.3 (4.0), respectively, and for the medication group ($n = 11$) were 8.7 (1.9), 7.7 (1.6), 8.8 (1.3), and 9.0 (1.5), respectively. Neither the main effect of medication status nor interaction of hemisphere with medication status was statistically different ($p > .20$ in all cases). The small group sizes make conclusions impossible, but it appears that the effects of medication per se cannot account for the differences between the NC and BPD groups. (For an extensive review of drug effects on the amygdala, see Davis [2000]).

**AXIS I DIAGNOSIS.** Another potential confound concerns the presence of co-occurring DSM-IV Axis I disorders. To examine possible contributions of frequently co-occurring Axis I disorders that were active in our study group (MDD and PTSD), differences between subgroups of the BPD patients defined by each co-occurring disorder were analyzed. In the BPD group, seven patients were diagnosed with active MDD, seven had no history of MDD, and one patient had a history of MDD. Amygdala activation levels to the neutral, happy, sad, and fearful expressions for the seven patients with active MDD and the seven patients without any history of MDD are shown in Figure 6 (along with the NC group for comparison). Neither the main effect of MDD status nor the interaction of hemisphere with MDD status was significant ($p > .30$ in all cases). Seven BPD patients were diagnosed with active PTSD, seven had no history of PTSD, and one had a history of PTSD (not active). Amygdala activation for the seven patients with active PTSD and the seven patients without a history of PTSD are shown in Figure 7. The main effect of PTSD status was not significant ($p > .40$). Although the PTSD status × hemisphere interaction did
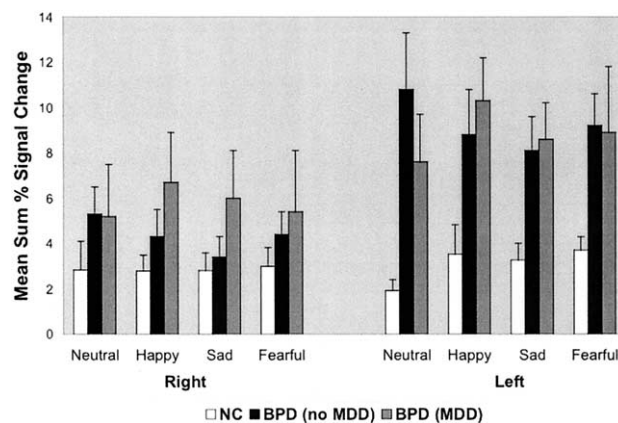


Figure 6. Mean levels of right and left amygdala activation for the borderline personality disorder (BPD) patients with active major depressive disorder (MDD) ($n = 7$) and without MDD ($n = 7$). Error bars show the SEM. NC, normal control.

not reach conventional levels of significance [$F(1,12) = 3.36$, $p = .09$], the trend suggested that amygdala hyperreactivity was bilateral for BPD subjects without PTSD and lateralized for those with PTSD.

As can be seen in Figures 6 and 7, within this sample of subjects there is no evidence that the co-occurring Axis I disorders of MDD and PTSD could account for the differences in left amygdala activation levels between the NC and BPD group.

## Discussion

The amygdala is one of the most studied brain regions in behavioral neurobiology and is thought to be a critical
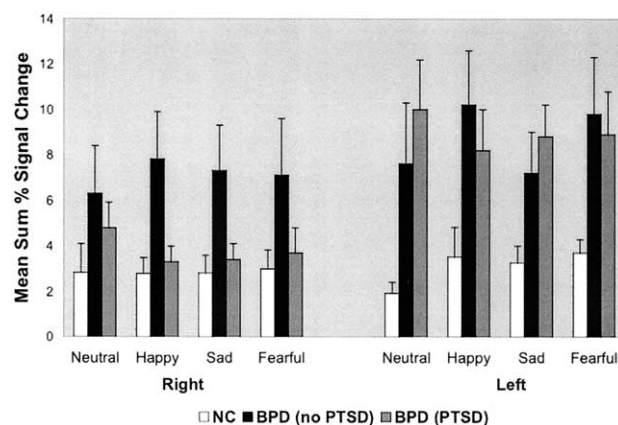


Figure 7. Mean levels of right and left amygdala activation for the borderline personality disorder (BPD) patients with active posttraumatic stress disorder (PTSD) ($n = 7$) and without PTSD ($n = 7$). Error bars show the SEM. NC, normal control.

element in the systems that generate fear/anxiety and the systems that modulate vigilance. Our finding, that left amygdala reactivity is abnormal in BPD patients (compared with NC subjects), is consistent with findings that the amygdala is also hyperreactive in mood and anxiety disorders (Drevets 1998; Rauch et al 2000; Thomas et al 2001) and consistent with animal laboratory studies on emotional regulation and dysregulation. Among the strengths of the present study, the subjects in both groups underwent comprehensive diagnostic assessment to ensure that the attributes of each group were well defined. Subjects in the NC group were, from a diagnostic standpoint, the more homogeneous, with stringent exclusion criteria to rule out all subjects with traces of Axis I and Axis II mental disorders. Although those in the BPD group were also carefully assessed, many of these subjects met criteria for other types of personality and mental disorders. (Another strength is the group size, i.e., 15 subjects per group.)

The presence of co-occurring disorders is illustrative of the heterogeneity of BPD. Consequently, our results could be affected by related psychopathologies, such as anxiety or depressive disorders. Our post hoc analyses suggest this to be unlikely in the case of group differences in left amygdala activation levels; however, although the PTSD status × hemisphere interaction did not reach conventional levels of significance, the pattern did suggest that amygdala reactivity might be bilateral for BPD subjects without co-occurring PTSD and lateralized to the left hemisphere for subjects with PTSD. This trend underscores the potential importance of assessing for co-occurring PTSD, and it will be important to follow up on this trend with sample sizes having adequate statistical power to replicate or reject this finding. The larger issue is that, until the neuropathologies of these disorders defined by clinical description are elucidated, it will be difficult to distinguish co-occurrence from co-morbidity (the latter implying a distinct neuropathology [Grilo et al 2000; McGlashan et al 2000]).

The rate of co-occurring Axis I and II disorders found in our study group was in line with that found in other clinical samples (McGlashan et al 2000; Zanarini 1998a, 1998b). As such, it is a more representative group of BPD patients; BPD samples without Axis I co-occurring disorders are highly atypical, and "pure" BPD clinical samples are rare, if they exist at all. Because of this, clinical research in BPD presents a conundrum. Although co-occurrence increases diagnostic noise for studies of pathophysiology, it also renders findings far more generalizable. Our strategy has been to be inclusive and, through post hoc analyses, to generate hypotheses about the effects, if any, of particular comorbidities on results. Our analysis here suggests that our amygdala/BPD findings are quite robust

and, with the possible exception of PTSD, relatively independent of diagnostic co-occurrence. An important objective of future studies will be to run comparison groups that have Axis I disorders, such as MDD or PTSD but not BPD, to characterize the ways in which their amygdala activation differs from BPD patients with MDD or PTSD. These efforts are part of our ongoing program of research.

Another limitation was that not all of our subjects were medication free, raising the question of whether the observed left amygdala hyperreactivity was to some degree a product of medication rather than the disorder; however, post hoc analyses suggest that the medications did not accentuate group differences. It will be important for future work to test these possibilities by employing medication washout procedures.

A further understanding of the hyperreactive left amygdala response to facial stimuli in BPD patients will require identifying the stimulus attributes controlling amygdala activation and the cognitive and behavioral processes to which the activation is contributing. As can be seen in Figure 5, the BPD group-means show similar levels of left amygdala activation to the four facial expressions compared with the fixation point, which raises a question about the stimulus specificity of the left amygdala response. An objective of future work will be to determine the classes of stimuli that do and do not elicit abnormal levels of amygdala activation in BPD patients. For example, one could determine the effectiveness of the facial expressions relative to pictures of nonsocial stimuli of various emotional valence (e.g., attacking animals, furniture, scenic views).

The similar levels of amygdala activation also raise the question of whether BPD patients are impaired in discriminating between various facial expressions of emotion relative to healthy individuals. In a study in which the Ekman faces were used, Wagner and Linehan (1999) found that, compared with healthy control subjects, BPD patients were able to identify human facial expressions accurately in all cases except for neutral faces (the same stimuli that we have used), for which they tended to make errors and consigned negative emotions to those faces. In the present study, the most striking difference between the BPD and NC groups was the much greater incidence of BPD patients projecting negative attributes onto the Ekman faces. This was most noticeable in the responses to the neutral faces (e.g., "They look like mug shots, like someone who just got arrested," "They look fake, like a façade—they are hiding something," "They look like they are plotting something.") It is also notable that several of the BPD patients reported that during the imaging session they were trying to figure out what the individuals with neutral expressions were thinking.

These observations are consistent with the proposals of Whalen (1998) and Amaral (2002) that one function of the amygdala is to increase vigilance and to facilitate an individual's evaluation of the threat potential of novel or ambiguous situations. Interestingly, in evaluating the ambiguous "neutral" expressions, some of the BPD subjects disambiguated these expressions by projecting emotions/intentions into their descriptions of the neutral faces. A potentially important feature of their attributions is that they were uniformly negative, threatening, and untrustworthy. These subjects' strong reactions to the neutral faces are consistent with the notion of transference.

It is important to recognize that BPD patients typically function closest to normal subjects in highly structured situations and have shown higher levels of psychopathology in unstructured testing situations (e.g., O'Leary and Cowdry 1994) and unstructured clinical settings (e.g., Judd and McGlashan 2003). We surmised that imaging BPD patients in a context of low structure would maximize the likelihood of BPD subjects processing the faces pathologically. The level of imposed structure/task is a variable we will systematically manipulate in future imaging studies (e.g., Lange et al 2003).

The results of this study suggest that the substantial amygdala activation elicited by the facial expressions in BPD patients is likely to be a key component of their emotional vulnerability, especially in the context of disturbed interpersonal relations and the crucial role of the amygdala in processing emotional stimuli and reactions. Our results suggest that the Ekman faces set has the potential to tap into relevant phenomenologic aspects of the psychopathology of BPD, because facial expressions of emotion should be an especially salient stimulus dimension for BPD patients, given that they provide nonverbal cues about the intentions and evaluations of others. We speculate that a hyperreactive amygdala could predispose BPD individuals to be hypervigilant and especially overreactive to others' emotional expressions and/or a perceived ambiguity in the attitudes of others. In social interactions, the borderline patient's emotional hyperresponsiveness can elicit unambiguous apprehensive avoidant (or aggressive) reactions in others, "confirming" the borderline individual's suspicions (projective identification). This now clearly negative signal from others could in turn elicit abnormally high levels of amygdala activity in the patient that engages the "fight or flight" system and generate "inappropriate, intense anger" (DSM-IV criterion 8, p. 654 [American Psychiatric Association 1994]), and "frantic efforts to avoid real or imagined abandonment" (DSM-IV criterion 1, p. 654 [American Psychiatric Association 1994]), and other features of emotional dysregulation that significantly impair interpersonal relationships. In contrast to a range of other perturbation procedures, such

as photographs of aversive nonsocial stimuli (e.g., attacking animals from the 1998 International Affective Picture System series), stimuli with an interpersonal context seem to proxy encounters that might elicit distress in BPD patients. Compared with noninterpersonal stimuli, the human face stimuli seem to be an especially informative assay of the abnormalities in neural functioning in BPD.

Finally, it is important to remember that the amygdala is a component of a complex, highly interconnected set of brain structures. The manifestations of emotional states are the products of patterns of activation within the entire system and the manner in which the individual interacts with the outside environment. The challenge is to characterize this system and identify how functional impairments in particular components dysregulates the system, and consequently, emotional states and behavior, especially those having adverse interpersonal consequences. Our results suggest that we have identified a link between emotionally laden stimuli in the environment and a key component of this system, the amygdala.

Our results also indicate that we have developed a sensitive procedure/probe capable of eliciting robust differences in patterns of brain activity between NC subjects and individuals with BPD, particularly in structures thought to be involved in modulating vigilance and generating negative emotional states. Findings from this study provide a foundation for elucidating the neural substrates of behavioral and emotional facets of BPD that contribute to disturbed interpersonal relations. These robust group differences also suggest that our procedures might prove to be a powerful tool for indexing and evaluating effects of current and new treatment approaches (e.g., dialectical behavior therapy, pharmacologic therapy, and radial transcranial magnetic stimulation therapies). Future challenges include identifying abnormalities within systems responsible for hypervigilance and emotional dysregulation and demonstrating how these systems interact to affect (or, are affected by) interpersonal relationships.

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