Neural correlates of emotion processing in borderline personality disorder


Article history:
Received 20 August 2007
Accepted 4 July 2008

Keywords:
Affective instability
Emotion
fMRI
Social–emotional cues
Borderline personality disorder

1. Introduction

Emotional instability is one of the most striking features of borderline personality disorder (BPD) and is central to many of the behavioral and interpersonal symptoms of the disorder (Stone, 1988; Linehan, 1993), including some of the most disabling, even life-threatening, symptoms of BPD, such as suicidality, outbursts of intense anger, stormy relationships, and identity disturbances (Koenigsberg et al., 2001). This emotional instability may be related to a heightened attention or sensitivity to social–emotional cues in interpersonal scenarios (Wagner and Linehan, 1999; Meyer et al., 2004; Taylor and Fragopanagos, 2005; Lynch et al., 2006), a tendency to self-referential emotional processing (Schnell et al., 2007), or to dysregulated emotional processing mechanisms (Phillips et al., 2003b). Understanding the nature of the disturbances in emotion processing in BPD may provide important insights into the mechanisms of affective instability, the underlying pathology of the disorder, understanding disorder, and the relationship between BPD and the Axis I mood disorders, as well as helping to identify endophenotypes that could focus genetic studies of BPD, and target biological or psychological treatments to more specifically address affective instability in BPD.

Neuroimaging studies have begun to identify networks that are engaged in emotion processing in healthy individuals and in those with disturbed affect. A number of studies have employed images from the International Affective Pictures System (IAPS; Lang et al., 2001) as emotional stimuli. The IAPS is a set of positive, negative and neutral valence pictures for which normative data for picture valence and arousal level are available. In healthy individuals, viewing of emotional pictures is associated with activation in the visual cortex (Takahashi et al., 2004; Britton et al., 2006), ventromedial prefrontal cortex and medial orbitofrontal cortex (Northoff et al., 2000; Takahashi et al., 2004; Britton et al., 2006; Grimm et al., 2006), anterior cingulate (Takahashi et al., 2004; Grimm et al., 2006), dorsolateral prefrontal cortex (Northoff et al., 2000; Grimm et al., 2006), amygdala-hippocampal region (Takahashi et al., 2004; Britton et al., 2006) and basal ganglia (Takahashi et al., 2004). Differences in activation patterns in these regions have...
been identified in schizophrenic subjects with and without affective flattening (Takahashi et al., 2004), phobics (Goossens et al., 2007), and individuals high in neuroticism (Britton et al., 2007).

Little is known about the neurobiological underpinnings of the emotional instability in BPD, but the BPD syndrome itself has been associated with regional hypometabolism and deficits in serotonergic activity (De La Fuente et al., 1997; Siever et al., 1999; Soloff et al., 2000; Leyton et al., 2001; New et al., 2002; Juengling et al., 2003). Structural magnetic resonance imaging (MRI) studies have found smaller amygdala, hippocampal (Driessen et al., 2000; Schmah et al., 2003; Tebartz van Elst et al., 2003), anterior cingulate (Tebartz van Elst et al., 2003; Hazlett et al., 2005) and orbitofrontal cortex (Tebartz van Elst et al., 2003) volumes in BPD patients compared with controls. Two functional neuroimaging studies of borderline patients performing an emotion–relation task have been reported. In the first, BOLD functional MRI (fMRI) was performed in six BPD patients and controls as they viewed negative or neutral pictures (inanimate objects). Compared with healthy controls, the BPD patients showed an increased activation of the amygdala bilaterally and of the medial and inferior lateral prefrontal cortex when viewing the negative versus the neutral images (Herpertz et al., 2001). The second study examined the processing of facial expressions of emotion (Donegan et al., 2003). The BPD patients showed increased left amygdala activation to fearful, sad, happy and neutral faces.

The emotional instability in BPD is associated with emotional reactivity to social events (Stiglmayr et al., 2005); yet the neuroimaging studies of emotion processing in BPD have thus far been confined to studies of face perception (Donegan et al., 2003) and to scenes intermixing social and non-social stimuli (e.g. images of attacking animals, offensive insects and reptiles, and disfigured bodies), making it impossible to characterize the processing of social cues in particular. This is a serious limitation since social and non-social emotional stimuli are processed differently in the brain (Britton et al., 2006). The present study represents an important advance because of its focus on social emotional processing in particular.

A network comprising the amygdala, fusiform gyrus, superior temporal sulcus (STS), primary visual regions, and the prefrontal cortex has been implicated in visual social emotional cognition (Allison et al., 2000; Adolphs and Spezio, 2006; Bokde et al., 2006). This model posits that visual social stimuli are processed by the fusiform face area in interaction with the STS, which attributes motivation and social intensity. Emotional salience is then assigned by the amygdala, together with other prefrontal areas such as the insula. The amygdala, via feedback loops to the STS and more primary visual areas, may activate attentional amplification (Allison et al., 2000) to relevant features of the stimuli. Building upon this formulation, Satpute and Lieberman (2006) have proposed a dual-process model of social cognition in which there is a division between “reflexive” and “reflective” neural systems. The former, including the amygdala, STS, orbitofrontal (OF) cortex, dorsal anterior cingulate (dACC) and basal ganglia, provides an automatic, fast operating emotional response, while the latter, incorporating the lateral and medial prefrontal areas, the medial temporal lobe and the rostral anterior cingulate (rACC), provides a more nuanced, experience-based, but slower-responding emotional appraisal. We hypothesize that the increased emotional reactivity characteristic of BPD patients may be a consequence of their inability to adequately engage the reflective system and thus to rely heavily upon the more primitive reflexive system. This model would imply that when processing social emotional stimuli, BPD patients compared with healthy subjects would show greater activation of the amygdala, fusiform gyrus, primary visual areas, STS, dACC and OFC, while healthy subjects would demonstrate greater activation of lateral and medial prefrontal areas and medial temporal regions compared with BPD subjects. To test these hypotheses, we obtained BOLD fMRI in BPD patients and healthy volunteers as they viewed social emotional pictures.

2. Methods

2.1. Subjects

Subjects were 19 BPD patients and 17 healthy volunteers (HC) recruited from the outpatient clinics at the Mount Sinai Medical Center in New York City, and the Bronx Veterans Affairs Medical Center, and by advertisements in local newspapers. They were male and female between 18 and 50 years of age. BPD subjects met DSM-IV criteria for BPD and had prominent affective instability as evidenced by the presence of three of four BPD criteria associated with affective instability (Koenigsberg et al., 2001), i.e. (1) affective instability due to a marked reactivity of mood, (2) chronic feelings of emptiness, (3) a pattern of unstable and intense interpersonal relationships, and (4) identity disturbance. BPD subjects could not meet DSM-IV criteria for present or past bipolar I disorder, schizophrenia, schizoaffective disorder, substance dependence, or organic mental syndromes, and could not have histories of significant head trauma, CNS neurological disease, or significant medical illness, or a substance abuse disorder within the previous 6 months. All subjects were free of psychotropic medication for at least 2 weeks (6 weeks in the case of fluoxetine) prior to the scan.

The healthy volunteers could not meet criteria for any current or past Axis I or Axis II disorder and could not have a family history of an Axis I disorder. Subjects with contraindications to MRI, pregnant women and patients with current active suicidal ideation were excluded.

All subjects received a physical examination, EKG, complete blood count, electrolyte, liver and renal function tests, thyroid function tests, urine analysis and a urine toxicity screen. The Structured Clinical Interview for DSM-IV (SCID-I/P) was utilized to evaluate Axis I diagnoses. The Schedule for Interviewing DSM-IV Personality Disorders (SIDP-IV) was utilized to evaluate criteria for DSM-IV personality disorders of interviews by Ph.D. or Master’s level psychologists with the patient and an informant close to the patient when available. In previous studies (Koenigsberg et al., 2002) we have documented an interrater reliability of kappa = 0.81 for diagnosing BPD. Subjects signed an informed consent after the study was explained to them.

As a measure of affective instability, subjects completed the Affective Lability Scale (ALS) (Harvey et al., 1989), a 54-item self-report scale which has been shown to correlate with clinician-rated affective instability in patients with BPD (Koenigsberg et al., 2002). Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971).

The two groups did not differ in age (BPD: 34.9±11.1 vs. HC: 31.2±10.6; t44 = 0.997, NS), or gender (BPD: 7 females vs. HC: 8 females; χ² = 0.39, NS). Both groups were primarily right-handed (BPD: 14 right-handed, 4 left-handed, 1 mixed; HC: 15 right-handed, 1 left-handed, 1 mixed; χ² = 1.834, df = 5, NS). Seven BPD subjects had a past history of major depression; none met criteria for a current major depressive episode. One BPD subject met criteria for current bipolar II disorder. Six subjects had a history of PTSD, of whom four currently met PTSD criteria. Comorbid personality disorders in the BPD sample included 11 subjects with paranoid personality disorders, seven with avoidant, four with antisocial, six with schizotypal, four with obsessive-compulsive, one with histrionic, and six with narcissistic personality disorders. Ratings on the Hamilton Depression Rating Scale indicated that the BPD patients were more depressed than the HC subjects, but their level of depression was mild (BPD: 9.38±4.86; HC: 1.33±0.89; t33 = 5.65, P < 0.001). Consistent with a higher level of affective instability, the BPD subjects attained a significantly higher total ALS scale score than the normal controls (BPD: 1.60±0.41 [range: 0.78–2.50] vs. HC: 0.31±0.25 [range: 0.00–0.81]; t34 = 11.20, P < 0.0001).

2.2. Experimental paradigm

Each subject viewed 25 negative and 25 positive pictures while BOLD fMRI images were acquired. Pictures were selected from the
Social positive, negative or neutral affective states. We selected pictures with a positive block. A blue screen bearing the word valence, with each individual image presented for 6 s. Five blocks of animals, reptiles or insects, or bodily deformity. The included images derived from non-interpersonal situations such as scenes of fearsome or more persons in interaction or one person emotionally relating to International Affective Pictures System (IAPS) (Lang et al., 2001), a collection of photographic images that have been induced to show positive, negative or neutral affective states. We selected pictures with social–emotional content by including IAPS pictures that showed two people being in interaction or one person emotionally relating to the viewer, and excluding those IAPS pictures whose negative valence derived from non-interpersonal situations such as scenes of fearsome animals, reptiles or insects, or bodily deformity. The included images were rated as high in either positive or negative valence and high in arousal, based upon the normative data provided for the IAPS (Lang et al., 2001).

The pictures were presented in blocks of five images of a given valence, with each individual image presented for 6 s. Five blocks of positive and negative images were presented in alternation beginning with a positive block. A blue screen bearing the word “relax”, the rest condition, appeared for 30 s before the first image block and between each positive and negative image block.

Subjects rested supine in the scanner and viewed the images via a set of fiber optic goggles (SV2000; Avotec, Inc.) positioned in the head coil above their eyes. They were instructed to keep their eyes open, to watch all images and to allow themselves to “feel fully whatever emotion the slides produced.” The subjects were also told that should they find any slide too disturbing, they could ask that the image be turned off. No subjects chose this option.

### 2.3. Manipulation check

Immediately following the scanning session, the subjects were asked to view, on a 15-in. laptop display, the IAPS pictures that they had seen during the scan and to rate their subjective reaction to each positive and negative image (5 images of 6-s duration). They were instructed to keep their eyes open, to turn off. No subjects chose this option.

After they completed the scan and to rate their subjective reaction to each positive and negative image (5 images of 6-s duration). They were instructed to keep their eyes open, to turn off. No subjects chose this option.

2.4. Image acquisition and analysis

MRI was performed on a Siemens 1.5 T Symphony scanner with enhanced (Quantum) gradients using the standard quadrature head coil. Following a localizer, anatomical images (T1 W) were acquired with a spin-echo sequence (TR/TE/FA 524/14/90, 20 axial 5-mm slices with 1.5-mm gap, FOV 220 mm, matrix 256×256). BOLD images were acquired at the same slices with single-shot EPI (TR/TE/FA 3000/60/90, matrix 64×64 with fat saturation); 220 BOLD images were acquired, but the first 10 were discarded to ensure magnetization steady-state and the last 10 were also discarded. Each block (10 BOLD images, 30 s) consisted of either a rest period or viewing of a negative or positive image (5 images of 6-s duration).

Image analysis was carried out using SPM5 (Wellcome Department of Cognitive Neurology, London, UK). Motion correction was applied by realigning all images to the first image using a six-parameter rigid body transformation and reslicing with 4th degree B-spline interpolation. The mean BOLD image was then spatially normalized with SPM5’s EPI template using both affine and non-linear normalization. Estimated normalization parameters are then applied to realigned BOLD images followed by 6-mm Gaussian kernel smoothing. Non-linear frequency cutoff, iterations, and regularization were set to 25 mm, 16, and 1, respectively. Following motion correction and temporal and spatial filtering, each subject was individually checked for image quality and analyzed for the contrasts: positive vs. rest, negative vs. rest, negative vs. positive, and positive vs. negative.

The first-level fixed-effects analysis included motion realignment parameters as regressors, and identified regions of significantly different BOLD activation in subjects viewing negative pictures vs. rest, positive pictures vs. rest, positive vs. negative pictures and negative vs. positive pictures. To test for differences between groups, we carried out a random-effects ANOVA design in each activation response (BPD=HC and HC>BPD) for the negative picture–rest (N–R), positive picture–rest (P–R), negative–positive picture (N–P), and positive–negative picture (P–N) contrasts. We repeated the same analyses entering handedness as a covariate (separate regressors for right and left handedness, where mixed handedness was defined as right and left handedness). The findings with and without the handedness covariate were essentially the same. For economy of space we present below the results of the analysis with handedness covared. These statistical tests employed a random-effects model, defining clusters with a voxelwise significance level of P=0.005 uncorrected and a minimum

### Table 1

<table>
<thead>
<tr>
<th>Region</th>
<th>k x y z T P</th>
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<tr>
<td>R cuneus/middle occipital gyrus (BA18)</td>
<td>82 16 −92 10 4.36 0.000</td>
</tr>
<tr>
<td>R superior occipital gyrus/cuneus (BA19)</td>
<td>22 32 −86 28 3.33 0.002</td>
</tr>
<tr>
<td>R middle occipital gyrus. (BA19)</td>
<td>26 48 −74 12 3.36 0.001</td>
</tr>
<tr>
<td>R middle occipital/temporal gyrus</td>
<td>57 30 −76 18 3.34 0.001</td>
</tr>
<tr>
<td>L superior temporal gyrus</td>
<td>48 −46 −42 16 3.45 0.001</td>
</tr>
<tr>
<td>R lingual gyrus (BA18/19)</td>
<td>28 18 −68 0 3.33 0.001</td>
</tr>
<tr>
<td>R precuneus/posterior cingulate</td>
<td>24 6 −66 18 3.51 0.001</td>
</tr>
<tr>
<td>R parahippocampal gyrus (BA19/30)</td>
<td>37 16 −48 0 3.24 0.001</td>
</tr>
<tr>
<td>R superior temporal gyrus infraparietal lobule (BA13)</td>
<td>87 46 −44 14 4.14 0.001</td>
</tr>
<tr>
<td>R middle frontal gyrus (BA6)</td>
<td>26 36 −2 48 3.33 0.001</td>
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### Table 2

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<tr>
<th>Region</th>
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<tr>
<td>R cerebellar declive</td>
<td>27 16 −76 −28 3.29 0.001</td>
</tr>
<tr>
<td>R middle occipital gyrus (BA19)</td>
<td>36 48 −70 −14 3.76 0.000</td>
</tr>
<tr>
<td>L middle/superior temporal gyrus (BA39)</td>
<td>42 −54 −64 22 3.62 0.000</td>
</tr>
<tr>
<td>R/L superior frontal gyrus (BA6)</td>
<td>45 4 6 64 4.19 0.000</td>
</tr>
<tr>
<td>L inferior frontal gyrus (BA45/47)</td>
<td>24 −54 22 6 3.56 0.001</td>
</tr>
<tr>
<td>L thalamus (ventral lateral nucleus)</td>
<td>29 −16 −12 4 3.83 0.000</td>
</tr>
<tr>
<td>Posterior cingulate (BA23)</td>
<td>40 0 −62 14 3.61 0.001</td>
</tr>
<tr>
<td>L inferior frontal gyrus (BA47)</td>
<td>46 −40 24 2 3.34 0.001</td>
</tr>
<tr>
<td>R lingual gyrus (BA19/30)</td>
<td>21 18 −50 0 3.22 0.001</td>
</tr>
<tr>
<td>R superior temporal gyrus</td>
<td>21 48 −40 16 3.09 0.002</td>
</tr>
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Clusters of activation for 20 contiguous voxels with local maxima of t>2.74, P<0.005 uncorrected. k = cluster size in voxels, xy,z are MNI coordinates of local voxel with maximum t, t=t-score of local maximum, P=P-value of that local maximum voxel, R=right, L=left.

1 The negative stimuli presented were IAPS picture nos. 2205, 6560, 9810, 6311, 6510, 2900, 2053, 6315, 2800, 3350, 6540, 6313, 3015, 9433, 9040, 9800, 3230, 6020, 6530, 6570, 3181, 3301, 6312, 6821, 6370, and the positive stimuli nos. 2360, 2091, 2020, 2340, 2500, 2550, 4700, 2530, 2391, 2341, 2050, 8200, 8033, 2540, 8470, 8120, 7325, 5831, 4614, 5470, 2080, 2650, 1340, 2370, 2501.
cluster size of $k=20$ voxels. Final anatomical labeling of findings in MNI space was based on the MSU Matlab toolbox (http://www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html).

Additional procedures were carried out for analysis of amygdala and fusiform activation, due to their importance for our a priori hypotheses and their isolation by previous authors as relevant structures. We assessed their activation by three separate methods. First, we relaxed the overall SPM second-level (random-effects) analysis to a voxel significance threshold of 0.10, within a cluster size of $k=10$, to search for clusters anatomically belonging to the amygdala and fusiform gyrus. Such clusters were found in the left amygdala (at coordinates $-16, -6, -14$, with $18$ contiguous voxels) and right fusiform (coordinates $42, -12, -32, 22$ voxels). We then conducted the SPM small volume correction as suggested by previous authors, with a $12$-mm diameter sphere for the amygdala (Strange and Dolan, 2004) and a $20$-mm diameter sphere for the fusiform gyrus (Winston et al., 2002). Second, we extracted the signal magnitude, defined by the contrast image intensity of each subject, at the original cluster voxels, averaged them, and subjected this mean VOI signal to additional tests. Finally, we defined anatomical VOIs on both right and left amygdala and fusiform gyrus, using the Wake–Forest University digital atlas (Maldjian et al., 2003), averaged the signal magnitude in those anatomical VOIs, and subjected them to statistical analyses. These numbers extracted from contrast images define the difference in the slope fitted with HRF “$\beta$(Negative)$-\beta$(Rest)”. Thus Positive and negative values refer to “$\beta$(Positive)$-\beta$(Rest)” and “$\beta$(Negative)$-\beta$(Rest)”, respectively.

3. Results

3.1. Self-report

The manipulation check confirmed that the positive and negative pictures elicited emotional reactions of the expected valence. For the BPD subjects, the mean SAM valence rating for the negative pictures was $7.18\pm0.19$ and $3.63\pm0.17$ for the positive pictures. The healthy controls rated the negative pictures at $7.49\pm0.19$ and the positive pictures at $3.50\pm0.17$. A repeated measures analysis of variance (ANOVA) with SAM valence rating as the dependent variable, IAPS picture valence category (positive vs. negative) as the within-subjects variable, and diagnosis as the between-subjects variable, and diagnosis as the between-subjects variable revealed a main effect for picture valence category ($F_{[1,33]}=259.0$, $P<0.0001$).

![Figure 1](image_url)

**Fig. 1.** Regions in which patients with borderline personality disorder (BPD) show a greater Negative Picture vs. Rest activation than healthy controls (BPD > HC) and healthy controls show a greater Negative Picture vs. Rest activation than BPD patients (HC > BPD). MFG-middle frontal gyrus, Cun-cuneus, STG-superior temporal gyrus, IPL-intraparietal lobule.
but no diagnosis × valence category interaction (F[1,33] = 0.85, NS), nor a main effect of diagnosis. Post hoc t-tests showed that within each group the positive and negative picture ratings were significantly different, confirming that subjects within each group differentiated the positive from negative IAPS pictures.

The negative pictures were more arousing than the positive pictures for both groups. The BPD subjects rated their subjective level of arousal for the negative pictures at 6.00 ± 0.29 and for the positive pictures at 4.71 ± 0.27. The healthy controls rated their arousal to the negative pictures at 6.40 ± 0.30 and to the positive pictures at 4.64 ± 0.28. Repeated measures ANOVA demonstrated a main effect in arousal for picture valence category (F[1,33] = 27.91, P = 0.000008), without a main effect of diagnosis or an interaction. Post hoc tests showed the differences were significant within each group as well. In the debriefing, all subjects reported that their reactions to the pictures in the immediate post-scan rating session were similar to their reactions while viewing the pictures during the scan.

### 3.2. BOLD activation

To compare patterns of brain activation between BPD patients and HCs as they viewed emotional stimuli, we obtained statistical maps of the difference in BOLD response when viewing negative pictures compared with rest (N–R) and when viewing positive pictures compared with rest (P–R) for BPD subjects and healthy controls. For each of these contrasts, we examined the between-group differences (i.e., BPD > HC and HC > BPD) (Tables 1 and 2; Figs. 1 and 2). Examination of the difference in BOLD activation when subjects viewed negative compared with positive emotional scenes (N–P) permitted subtracting out the effects of looking at faces and social scenes. The between-group differences for the N–P contrast are presented in Table 3.

The BPD patients demonstrated a greater difference in BOLD activation to negative pictures vs. rest than the healthy controls in the primary visual areas (BA18, BA19), premotor cortex (BA6), superior temporal gyrus (STG), and middle temporal gyrus (MTG).

![Fig. 2. Regions in which BPDs show a greater Positive Picture vs Rest Activation than Healthy Volunteers (BPD > HC) and Healthy volunteers show a greater Positive Picture vs. Rest Activation than BPDs (HC > BPD). MTG—Middle Temporal Gyrus, STG—Superior Temporal Gyrus.](image-url)
When neither the gender main effect nor the interaction reached significance, the magnitude of differences was only significant in an ANOVA of diagnosis by gender, only diagnosis reached significance (interactions with diagnosis, only diagnosis was significant). BPD patients showed a greater difference than the healthy controls when gender was controlled ($t_{34}=3.20$, $P=0.005$). The BPD patients also showed a greater difference in BOLD activation in the amygdala and fusiform gyrus than the healthy controls. The amygdala plays a central role in assessing emotional salience, in face processing and in the generation of an affective state, and is particularly reactive to aversive stimuli (Phillips et al., 2003a; Dickstein and Leibenluft, 2006). The fusiform cortex is implicated in face processing as well. The finding of a greater N–R difference in BOLD activation in BPD patients than in the healthy controls in the left amygdala and fusiform gyrus is consistent with the findings of Hetpertz et al. (2001) and Donegan et al. (2003). Activation of the left amygdala in particular has been associated with the viewing of sad or fearful faces (Lane et al., 1997b). The BPD patients also showed a greater N–R BOLD difference than the healthy controls in primary visual processing areas (the middle occipital gyrus, the cuneus, and the lingual gyrus). This is consistent with an upregulation of the visual processing stream in response to feedback from the amygdala, which has projections to the visual cortex (Morris, 2004; Vuilleumier et al., 2004; Taylor and Fragopanagos, 2005). Thus one possible interpretation of our finding is that in the presence of negative visual emotional stimuli, BPD patients enhance the activation of primary visual processing regions. Duncan and Barrett (Duncan and Barrett, 2007) have suggested that heightened visual activation may allow individuals to be aware of affective stimuli that may be invisible to others. Such a neural mechanism could account for the finding that borderline patients have a heightened visual sensitivity to identifying facial expressions of emotion (Wagner and Linehan, 1999; Lynch et al., 2006). This intriguing idea raises the possibility that borderline patients’ exquisite interpersonal sensitivity may be related to a hyperawareness of facial expression or other social cues.

Further along in the visual processing stream, BPD patients show greater N–R and P–R differences in BOLD activation than healthy controls in the superior temporal gyrus (STG). The STG is implicated in the processing of human actions and in the assessment of intentions (Allison et al., 2000) and is considered to be part of a fast-response, phylogenetically older, and more reflexive social processing system (Satpute and Lieberman, 2006). When processing negative pictures compared with rest, the healthy controls showed a greater difference in activation than the BPD patients in BA46, a dorsolateral prefrontal region involved in reflective cortical processing and executive control. Although these observations require replication, they raise the possibility that, when processing social–emotional cues, BPD patients rely more upon reflexive, automatically responding networks, whereas healthy volunteers call upon networks with access to higher level conscious cortical processing. The BPD patients also showed greater N–R and P–R differences in activation in the precuneus and posterior cingulate than the healthy controls did. The precuneus and posterior cingulate are implicated in the processing of emotional information (Allison et al., 2000) and are considered to be part of a fast-response, phylogenetically older, and more reflexive social processing system (Satpute and Lieberman, 2006). When processing negative pictures compared with rest, the healthy controls showed a greater difference in activation than the BPD patients in BA46, a dorsolateral prefrontal region involved in reflective cortical processing and executive control. Although these observations require replication, they raise the possibility that, when processing social–emotional cues, BPD patients rely more upon reflexive, automatically responding networks, whereas healthy volunteers call upon networks with access to higher level conscious cortical processing. The BPD patients also showed greater N–R and P–R differences in activation in the precuneus and posterior cingulate than the healthy controls did. The precuneus and posterior cingulate are implicated in the processing of emotional information (Allison et al., 2000) and are considered to be part of a fast-response, phylogenetically older, and more reflexive social processing system (Satpute and Lieberman, 2006).
posterior cingulate have been implicated in self-referential processing and first person perspective (see Vogt, 2005 for review, see Cavanna and Trimble 2006), features consistent with the tendency for BPD patients to become emotionally overinvolved in interpersonal situations.

The healthy subjects demonstrated a greater difference in BOLD activation in the insula than the BPD patients when viewing negative pictures compared with rest and negative pictures compared with positive pictures. The insula is involved in the processing of facial emotion (Adolphs and Spezio, 2006) and in the subjective awareness of one’s emotional state (Craig, 2004). Recently, increased insula activation has been reported in trauma-exposed individuals who did not go on to develop PTSD, in contrast to similarly exposed subjects who developed PTSD (A. New, personal communication, May 2007). Thus insula activation may be associated with adaptive processing of emotional stimuli. The BPD patients show greater N−R and P−R differences in BOLD activation in premotor (BA6) regions than the healthy volunteers. The activation of these regions may be a marker of a readiness to act, which is consistent with the tendency of borderline patients to “act out” when confronted with strong emotional states. BPD patients show smaller activation differences in the caudate than healthy controls when viewing positive pictures compared with rest. Caudate activation is associated with pleasurable experience (Aron et al., 2005). BPD patients demonstrate greater P−R activation differences in the cerebellar declive than healthy controls. The cerebellum receives afferents from the parahippocampal and anterior cingulate cortices and the hypothalamus, has efferents to the prefrontal and cingulate cortices and the hypothalamus (Parvizi et al., 2001), and has been shown to participate in emotional processing (Lane et al., 1997a; Paradiso et al., 1999).

fMRI examines task-dependent activation differences within subjects rather than absolute BOLD values; hence the findings we report of increased activation differences in one group compared with the other may reflect an increased activation in the task condition (viewing negative or positive pictures), decreased activation in the rest state, or some combination of the two.

Strengths of the current study include the sample size, which is to our knowledge the largest sample of BPD subjects in an fMRI study of emotion processing. In addition, all subjects were unmedicated. Another strength of the present study is we have examined responses to social-emotional cues exclusively, excluding non-interpersonally related negative valence stimuli.

The present study has a number of limitations. The first results from our choice to contrast BOLD responses when viewing negative or positive pictures to the resting state rather than to the viewing of neutral pictures. This did not allow us to directly subtract out the effects of simply looking at complex scenes or faces. Despite this potential limitation, we chose the present design because we could not assure that borderline patients would perceive neutral pictures as such. A number of investigators have reported that BPD patients experience neutral faces as negative (Wagner and Linehan, 1999; Donegan et al., 2003), often attributing negative motives to neutral expressions. However, we did examine the BOLD negative minus positive (N−P) and positive minus negative (P−N) contrasts to obtain analyses which subtract out the effects of simply processing complex scenes and faces. Overall, we found the between-group comparison for the N−P contrast similar to our findings in the negative−rest contrast, with BPD patients showing greater N−P differences in activation than healthy controls in the amygdala, fusiform and primary visual regions, and healthy controls showing a greater N−P difference in the insula than the BPD patients. Thus, even when the effect of simply looking at scenes and faces is subtracted out, we find differences in BOLD activation between BPD and healthy control subjects in their differential response to negative versus positive social emotional scenes. A second potential limitation in the present study arises from the fact that negative valence IAPS pictures are more arousing than positive IAPS pictures. Thus the differences between BPD and healthy control subjects with respect to negative pictures could be attributed either to a differential response to valence or to arousal. An arousal effect, however, is unlikely to explain the group differences in processing the positive images, as they were not rated as highly arousing. Finally, since the BPD patients were, as is typical of clinical samples, more depressed than the healthy control subjects, we cannot exclude the possibility that the differences we find are related to depression rather than to the personality diagnosis. However, based on the mean Hamilton depression scores, the level of depression among the BPD patients in this sample was quite mild, close to the score typically used to identify remitted depressed patients (Thase and Ninan, 2002).

The present study suggests that BPD patients respond to negative and positive social emotional scenes with a hyperaroused visual processing system relative to healthy volunteers and with a more activated premotor cortex. In addition, when the stimuli are negative, BPD subjects appear to show greater activity in the amygdala, fusiform, precuneus and parahippocampal regions than healthy controls, who mobilize dorsolateral and insular regions instead. These findings are consistent with the model that borderline patients use a more reflexive, hypervigilant and action−prone system to process social emotional stimuli, whereas healthy volunteers call upon a more reflective and less reactive network. These observations may help explain the greater emotional reactivity of BPD patients.

Acknowledgements

This work was supported by Grant Number MO1-RR-00071 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and the Mental Illness Research, Education and Clinical Center, VISN 3 Veterans Health Administration, and an educational grant from the Siemens Medical Systems, Inc. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NCRR, NIH, or the VA. We thank Dr. Sergei Pakhomov (Institute of the Human Brain, St. Petersburg, Russia) for the MSU software.

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