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Neural correlates of emotion processing in borderline personality disorder ☆

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ABSTRACT

Emotional instability is a hallmark feature of borderline personality disorder (BPD), yet its biological underpinnings are poorly understood. We employed functional magnetic resonance imaging (fMRI) to compare patterns of regional brain activation in BPD patients and healthy volunteers as they process positive and negative social emotional stimuli. fMRI images were acquired while 19 BPD patients and 17 healthy controls (HC) viewed emotion-inducing pictures from the International Affective Pictures System set. Activation data were analyzed with SPM5 ANCOVA models to derive the effects of diagnosis and stimulus type. BPD patients demonstrated greater differences in activation than controls, when viewing negative pictures compared with rest, in the amygdala, fusiform gyrus, primary visual areas, superior temporal gyrus (STG), and premotor areas, while healthy controls showed greater differences than BPD patients in the insula, middle temporal gyrus and dorsolateral prefrontal cortex (BA46). When viewing positive pictures compared with rest, BPD patients showed greater differences in the STG, premotor cortex, and ventrolateral prefrontal cortex. These findings suggest that BPD patients show greater amygdala activity and heightened activity of visual processing regions relative to findings for HC subjects in the processing of negative social emotional pictures compared with rest. The patients activate neural networks in emotion processing that are phylogeneticall older and more reflexive than those activated by HC subjects.

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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 senarios (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

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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; Schmahl 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 inferolateral 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 intension. 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 (OFC) 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 toxicology 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-IV (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; $t_{34} = 0.997$, NS), or gender (BPD: 7 females vs. HC: 8 females; $\chi^2 = 0.39$, 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; $\chi^2 = 1.834$, $df = 5$, 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; $t_{23} = 5.65$, $P < 0.001$). 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]; $t_{34} = 11.20$, $P < 0.0001$).

2.2. Experimental paradigm

Each subject viewed 25 negative and 25 positive pictures while BOLD fMRI images were acquired. Pictures were selected from the