ARCHIVAL REPORT

Neural Correlates of Negative Emotionality in Borderline Personality Disorder: An Activation-Likelihood-Estimation Meta-Analysis

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Background: Emotional vulnerabilities at the core of borderline personality disorder (BPD) involve a dysfunction of frontolimbic systems subserving negative emotionality. The specific regions identified in individual studies, however, vary widely and provide an incomplete understanding of the functional brain abnormalities that characterize this illness. A quantitative synthesis of functional neuroimaging studies might clarify the neural systems dysfunctions that underlie negative emotionality in BPD.

Methods: An electronic search of Medline and PsycInfo databases from 2000 to 2012 identified 18 potential studies, of which 11 met inclusion criteria for the meta-analysis and comprised a pooled sample of 154 BPD patients and 150 healthy control subjects. Contrasts of negative versus neutral emotion conditions were analyzed with an activation-likelihood-estimation meta-analytic approach. Group comparisons were performed on study-reported between-subjects contrasts and independent subtraction analyses based on within-subjects contrasts.

Results: Healthy control subjects activated a well-characterized network of brain regions associated with processing negative emotions that included the anterior cingulate cortex and amygdala. Compared with healthy control subjects, BPD patients demonstrated greater activation within the insula and posterior cingulate cortex. Conversely, they showed less activation than control subjects in a network of regions that extended from the amygdala to the subgenual anterior cingulate and dorsolateral prefrontal cortex.

Conclusions: Processing of negative emotions in BPD might be subserved by an abnormal reciprocal relationship between limbic structures representing the degree of subjectively experienced negative emotion and anterior brain regions that support the regulation of emotion. Contrary to early studies, BPD patients showed less activation than control subjects in the amygdala under conditions of negative emotionality.

Key Words: Anterior cingulate cortex, borderline personality disorder, emotion regulation, functional magnetic resonance imaging, insula, negative emotionality

Borderline personality disorder (BPD) is a severe psychiatric illness affecting 1%–2% of the general population and upwards of 20% of psychiatric inpatients (1,2). Emotion dysregulation is a hallmark symptom of BPD, characterized by an unstable expression and more intense subjective experience of negative emotions (3,4). The neural basis of emotion dysregulation in BPD has been the subject of considerable scrutiny among neuroscientists, with the bulk of this research with functional magnetic resonance imaging (fMRI) to investigate negative emotionality in BPD (5,6). The processing of negative emotions in healthy individuals is subserved by a network of brain regions comprising the medial/ventral prefrontal cortex (PFC), subcallosal/anterior cingulate cortex (ACC), insular cortex, and amygdala (7,8). Given that individuals with BPD experience difficulties in the regulation of negative emotions, the task of elucidating which neural systems underlie these symptoms is critical for constructing a coherent neurobiological model of emotion dysregulation in BPD.

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Early fMRI studies of BPD presumed that biological vulnerabilities to emotional hyperreactivity might have their substrate in heightened neural activity in limbic structures (e.g., amygdala) that were understood to be involved in the subjective experience of negative emotions. Consistent with this hypothesis, Herpertz *et al.* (9) demonstrated elevated bilateral amygdala activity in six female BPD patients while they passively viewed highly arousing and unpleasant photographs. Following this work, Donegan *et al.* (10) measured activity within the amygdala in BPD patients while they viewed neutral, happy, sad, and fearful facial expressions and found higher activity in the left amygdala as compared with healthy control (HC) subjects. A series of subsequent investigations used a variety of paradigms to evaluate negative emotionality in BPD, including tasks that asked subjects to recall unresolved life events (11), use scripts to visualize episodes of self-injury (12), and employ a psychological distancing strategy to regulate emotional responses (13,14). The results of these studies revealed functional abnormalities in a network of brain regions extending beyond the amygdala to include the occipital cortex; dorsal ACC; and dorsolateral, orbital and medial PFC.

On the basis of these studies, narrative reviews of neuroimaging findings in BPD (15,16) have converged on a model of emotion dysregulation in this illness that implicates a dysfunction of two neural processes: a deficient regulatory control system operating through anterior brain regions (i.e., PFC, ACC) that show reduced engagement in functional neuroimaging studies; and a hyperresponsive subcortical limbic system that reflects heightened activity in specific neural structures (e.g., amygdala, insula) and might be associated with a subjectively more intense experience of negative emotions. According to this model, emotion dysregulation in BPD is thought to result from a failure of "top-down" frontal control pro-

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Table 1. Sample Characteristics of Studies Included in the Meta-Analysis

	Borderline Patients				Healthy Control Subjects		
Authors	*n*	Age	% Female	Patient Type	*n*	Age	% Female
Beblo *et al.* (11)	20	31.3	100	Inpatient	21	32.6	100
Guirtart-Masip *et al.* (66)	10	31.3	50	Outpatient	10	31.2	50
Herpertz *et al.* (33)	6	26.2	100	Inpatient	6	27.2	100
Koenigsberg *et al.* (21)	18	32.6	55.6	Outpatient	16	31.8	56.2
Kraus *et al.* (12)	11	25.6	100	Inpatient	10	25.6	100
Minzenberg *et al.* (67)	12	30.3	41.7	Outpatient	12	30.7	50
Schnell *et al.* (22)	14	28	100	Inpatient	14	28.4	100
Schulze *et al.* (48)	15	27.6	100	Inpatient	15	24.5	100
Silbersweig *et al.* (61)	16	31.2	93.8	Not applicable	14	23.8	71.4
Smoski *et al.* (68)	12	30.8	0	Outpatient	12	32.8	0
Wingenfeld *et al.* (69)	20	29.8	70	Outpatient	20	29.4	70
Total/Mean	154	29.5	73.7		150	28.9	72.5

cesses involved in modulating activity in over-reactive emotion-generating limbic structures.

A precise characterization of the neural systems abnormalities underlying negative emotionality in BPD, however, remains elusive. Integration of findings across individual studies is complicated by considerable variability in sample sizes, gender compositions, and psychiatric comorbidities, which limits the conclusions that might be drawn from any one study. The purpose of the current meta-analysis, therefore, was to quantitatively synthesize individual neuroimaging studies of negative emotionality in BPD so as to identify those neural structures that show the greatest functional abnormalities in this regard. We used an activation-likelihood-estimation (ALE) approach to examine differences in functional activation on a voxel-wise basis between BPD patients and HC subjects (17) and thereby provide a more coherent understanding of the neural systems subserving negative emotionality in BPD.

Methods and Materials

Study Selection

The electronic databases Medline and PsycInfo were searched with the key words "borderline" with independent matched searches with the key word(s) "borderline personality disorder," "functional magnetic resonance imaging," "fMRI," "neuroimaging," "neural," "imaging," "emotion," and "affect." The asterisk symbol (*) was used to incorporate all possible suffix variations of the search terms in study retrieval. Both English and non-English language articles were considered in the literature search. Articles were considered for inclusion in the meta-analysis if they met the following criteria: 1) publication between 2000 and 2012; 2) research designs that included within-subjects contrasts for BPD patients and/or between-subject contrasts for BPD patients versus HC; and 3) reported stereotactic coordinates (i.e., Talairach, Montreal Neurological Institute [MNI]) compatible with the meta-analysis software. If these three criteria were met, the article was required to meet certain standards. First, patients must have met diagnostic criteria for BPD according to the DSM (third edition or later) with a reliable and valid interview (e.g., Structured Clinical Interview for DSM-IV Axis II Disorders, International Personality Disorder Examination). Second, diagnostic co-occurrence of posttraumatic stress disorder (PTSD) must not have exceeded 50% of the patient sample. We chose to limit the extent of diagnostic comorbidity of PTSD to ensure a more homogeneous set of patients, given the distinct neural responses associated with PTSD when comorbid with BPD (18,19). Third, subjects must have completed a paradigm that included at least two conditions: 1) a negative emotion condition, and 2) a neutral comparison condition. Studies of pain perception and reward processing were excluded. Of the 18 fMRI studies initially identified in the literature search, 11 met criteria for inclusion in the meta-analysis. Excluded studies did not meet inclusion criteria for the following reasons: they did not report a negative emotion minus neutral contrast for either within- or between-subjects comparisons (18,20–25); solely region-of-interest (ROI) analyses were reported (10); at least 50% of patients were comorbid for PTSD (10,18); or the study was based on the same sample as a separate report included in the meta-analysis (26). The final combined sample included a total of 154 BPD patients and 150 HC (Table 1). We did not conduct separate ROI analyses (e.g., amygdala), because they were used in too few studies ($n = 3$).

Contrast Selection

Neuroimaging studies of negative emotionality in BPD employed a number of tasks (e.g., passive viewing, script-driven imagery) and evaluated a variety of contrasts among several task conditions. After examining these characteristics of individual studies, we selected for inclusion in the meta-analysis any neuroimaging study of BPD that investigated negative emotionality broadly defined (Table 2). By adopting this approach, we sought to evaluate as many relevant studies as possible while maintaining a reasonable level of homogeneity in our measurement of negative emotionality. Coordinates based on within-subjects and between-subjects contrasts of negatively valenced minus neutral emotion conditions were extracted and included in the meta-analysis. The inverse contrast was reported very infrequently in primary studies and thus was not further investigated. This approach resulted in four primary analyses: 1) within-subjects contrasts for BPD patients; 2) within-subjects contrasts for HC; 3) between-subjects contrasts for BPD $>$ HC; and 4) between-subjects contrasts for HC $>$ BPD. Two secondary analyses were conducted with the subtraction analysis method of GingerALE software version 2.1 to aggregate within-subject contrasts reported by individual studies to generate an independent between-subjects contrast (BPD $>$ HC and HC $>$ BPD). Following this data analytic approach, a total of 11 studies were included in the meta-analysis, 10 of which contributed to study-reported between-subjects contrasts and 6 of which contributed to within-subjects contrasts.

ALE Meta-Analysis

The GingerALE 2.1 BrainMap application (27) was used to generate quantitative voxel-wise ALE maps for the contrasts of interest. Input files of study foci were manually created for coordinate-based data in both Talairach and MNI spaces, although the final ALE anal-