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

Anthony C. Ruocco, Sathya Amirthavasagam, Lois W. Choi-Kain, and Shelley F. McMain

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.

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-
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-subjects 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-subjects 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-
ysis was performed in Talairach space. Any coordinates originally reported in MNI space were converted to Talairach space with the icbm2tal algorithm software (28). From this foci dataset, ALE values were computed for each voxel in the brain. These values in turn are used to calculate a three-dimensional Gaussian distribution of the ALE statistic at each voxel, blurring the coordinate data to correct for potential spatial uncertainty (29). This Gaussian distribution is defined by a predetermined full-width half-maximum outlined by Eickhoff et al. (27). The method used by GingerALE to create ALE maps is a form of random effects analysis, comparing above-chance differences in convergence. A permutation test was performed during the subtraction analysis with 5000 simulations to determine ALE significance at each individual voxel (29). In total, five ALE maps were created for the purposes of this study. Each map was thresholded with a false discovery rate-corrected threshold of \( p < .05 \) and a minimum cluster threshold of 100 mm\(^3\).

Results

Within-Subjects Contrasts

HC. Our ALE analysis of HC yielded seven clusters of activation that were dependent on five studies reporting negative—neutral contrasts. The right ACC (Brodmann area [BA] 32) contained three independent sites of activation that comprised the dorsal/midcingulate cortex and perigenual and subgenual ACC (Table 3). Significant foci of activation

### Table 2. Paradigm Descriptions and Contrasts Evaluated in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Paradigm Description</th>
<th>Between- and Within-Subjects Contrasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beblo et al. (11)</td>
<td>Recollection of resolved vs. unresolved life events</td>
<td>BPD &gt; HC, unresolved—resolved life events</td>
</tr>
<tr>
<td>Guiralt-Masip et al. (66)</td>
<td>Discrimination of negative vs. neutral faces</td>
<td>BPD &gt; HC, negative—neutral faces</td>
</tr>
<tr>
<td>Herpertz et al. (33)</td>
<td>Perception of highly arousing unpleasant vs. neutral photographs</td>
<td>BPD &gt; HC, negative—neutral photographs</td>
</tr>
<tr>
<td>Koenigsberg et al. (21)</td>
<td>Perception of photographs portraying aversive (negative) vs. neutral interpersonal situations</td>
<td>HC &gt; BPD, negative minus neutral</td>
</tr>
<tr>
<td>Kraus et al. (12)</td>
<td>Script-driven imagery to induce a negative vs. neutral emotional state</td>
<td>BPD &gt; HC, negative minus neutral script</td>
</tr>
<tr>
<td>Minzenberg et al. (67)</td>
<td>Photographs of faces with angry, fearful and neutral expressions</td>
<td>BPD &gt; HC, fear minus neutral</td>
</tr>
<tr>
<td>Schnell et al. (22)</td>
<td>Perception of negatively valenced drawings vs. neutral photographs</td>
<td>HC, negative minus neutral</td>
</tr>
<tr>
<td>Schulze et al. (48)</td>
<td>Viewing of negative vs. neutral photographs</td>
<td>BPD, negative minus neutral</td>
</tr>
<tr>
<td>Silbersweig et al. (61)</td>
<td>Emotional lexical go/no-go task</td>
<td>HC &gt; BPD, negative minus neutral for no-go trials</td>
</tr>
<tr>
<td>Smoski et al. (68)</td>
<td>Emotional “oddball” task containing neutral and negative photographs</td>
<td>BPD &gt; HC, negative minus neutral for no-go trials</td>
</tr>
<tr>
<td>Wingenfeld et al. (69)</td>
<td>Emotional Stroop containing words that were neutral, generally negative, or related to a past negative life event</td>
<td>HC &gt; BPD, negative minus neutral</td>
</tr>
</tbody>
</table>

BPD, borderline personality disorder; HC, healthy control subjects.
were also found bilaterally in the amygdala (Figure 1). Table 4 provides the weighted center and cluster size for each ALE-based activation site.

**Borderline Personality Disorder.** A total of five studies reported the within-subjects contrast of negative emotion minus neutral for BPD patients. Our ALE analysis of these studies elicited eight clusters of activation (Table 2). The largest clusters encompassed the dorsal ACC, predominantly on the left side. There were also significant clusters of activation isolated to the right medial (BA 9) and dorsolateral PFC (BA 8), left superior temporal gyrus (BA 38), and left posterior cingulate (BA 30) and a single cluster encompassing both the anterior culmen and posterior declive of the cerebellum (Figure 1).

### Between-Subjects Contrasts

**Study-Reported Between-Subjects Contrasts.** Ten studies reported between-groups contrasts for negative—neutral experimental conditions for BPD patients as compared with control subjects. These contrasts produced areas of activation consistent with those observed in within-subjects contrasts for the respective groups. The ALE-based contrast of BPD patients—control subjects revealed greater activation for BPD patients bilaterally within the posterior cingulate gyrus, right insula, and left inferior frontal gyrus (Table 5). Conversely, BPD patients showed less activation than control subjects in the bilateral dorsolateral PFC, right subgenual and dorsal ACC, right amygdala, and left superior temporal gyrus.

**Independent Subtraction Analysis.** We conducted a separate between-groups contrast of negative—neutral task conditions on the basis of the lower-level within-subjects contrasts reported separately for BPD and HC in individual studies. With the GingerALE 2.1 subtraction analysis feature, we found that BPD patients showed less activation within a single pronounced cluster bilaterally in the subgenual ACC (BA 25), which also corresponded with the results of study-reported between-subjects contrasts. No significant areas of activation were revealed in the contrast of BPD—HC.

### Discussion

Difficulties in the regulation of negative emotions represent a hallmark feature of BPD. Neuroimaging has increasingly been used to understand the neural systems dysfunctions that underlie negative emotionality in BPD, with narrative reviews of this literature suggesting abnormally heightened activity in limbic structures and reduced activation of anterior brain regions during negative emotion processing in this illness (31). Findings across individual studies are highly discrepant, however, perhaps due to variations in meth-

![Figure 1. Activation-likelihood-estimation contrast maps of negative emotion—neutral for control subjects (top row), borderline personality disorder (middle row) and borderline personality disorder—control subjects (bottom row). Maps are based on a false discovery rate-corrected threshold of p < .05 and a minimum cluster threshold of 100 mm³. Areas showing higher activation are in red; lower activation in blue.](image)

Table 4. Within-Subjects Contrasts of Negative Emotion—Neutral Conditions for Borderline Personality Disorder

<table>
<thead>
<tr>
<th>Cluster Size (mm³)</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Hemisphere</th>
<th>Anatomical Region</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>656</td>
<td>−13</td>
<td>31</td>
<td>26</td>
<td>Left</td>
<td>Cingulate gyrus</td>
<td>32</td>
</tr>
<tr>
<td>344</td>
<td>11</td>
<td>27</td>
<td>26</td>
<td>Right</td>
<td>Anterior cingulate</td>
<td>32</td>
</tr>
<tr>
<td>336</td>
<td>15</td>
<td>41</td>
<td>14</td>
<td>Right</td>
<td>Medial frontal gyrus</td>
<td>9</td>
</tr>
<tr>
<td>320</td>
<td>−44</td>
<td>11</td>
<td>−31</td>
<td>Left</td>
<td>Superior temporal gyrus</td>
<td>38</td>
</tr>
<tr>
<td>288</td>
<td>−41</td>
<td>−51</td>
<td>−20</td>
<td>Left</td>
<td>Anterior culmen and posterior declive</td>
<td></td>
</tr>
<tr>
<td>152</td>
<td>−20</td>
<td>−54</td>
<td>14</td>
<td>Left</td>
<td>Posterior cingulate</td>
<td>30</td>
</tr>
<tr>
<td>112</td>
<td>53</td>
<td>7</td>
<td>37</td>
<td>Right</td>
<td>Middle frontal gyrus</td>
<td>8</td>
</tr>
</tbody>
</table>

BA, Brodmann area.
odology (i.e., activation tasks employed, aural vs. visual task presentation) and sample characteristics (i.e., diagnostic comorbidity, clinical severity of patients). The purpose of the present study, therefore, was to quantitatively synthesize individual neuroimaging studies of negative emotionality in BPD with the aim of identifying more consistent patterns of functional activation in this patient group.

We examined the contrast of negative—neutral task conditions in control subjects and found expected patterns of activation that encompassed the amygdala, midcingulate cortex, and perigenual and subgenual ACC. These findings are consistent with established brain regions known to be involved in negative emotion processing in healthy individuals (7). The BPD patients also activated the ACC, particularly within the dorsal region, as well as the medial and dorsolateral PFC, superior temporal gyrus, posterior cingulate, and cerebellum. These widespread areas of activation suggest that BPD patients might engage a more diffuse network of neural structures associated with negative emotion processing.

Compared with control subjects, BPD patients had significantly reduced areas of activation in a complex of brain regions extending from the amygdala to the superior temporal cortex, ACC, and dorsolateral PFC. The amygdala has been reported as showing excessive activity in BPD patients relative to control subjects (32), particularly in early work that used ROI analyses to measure the extent of neural activation in this structure (10). Inspection of the few individual studies that did detect increased amygdala activation in BPD patients suggested that these findings could be related to differences in sample characteristics and task methodology. For example, Herpertz et al. (33) studied only six BPD inpatients with a fixed-effects statistical analysis, and Donegan et al. (10) subtracted crosshair fixation (rather than a neutral emotion condition) from negative facial emotion slides, and nearly all BPD patients had a current major mood disorder including bipolar I disorder. Although the amygdala represents a neural structure susceptible to inhomogeneities in the magnetic field that could cause signal dropout and reduce the sensitivity of the blood oxygen level–dependent signal in echo-planar FMRI imaging (34), there is no reason to suspect that BPD patients would be systematically more prone to this issue than control subjects, which as a group demonstrated consistent amygdala activation in response to negative emotions in this study. Additionally, a reduction of neural activity in the amygdala is more consistent with structural brain imaging studies, which show a robust 13% reduction in the volume of this structure bilaterally in BPD patients (35).

The results of this ALE meta-analysis identified the right insular cortex as showing heightened activity in BPD patients as compared with control subjects. The insula is considered a critical structure involved in representing the degree of subjectively experienced negative emotion (36), especially disgust (37). This structure has efferent connections to many regions that showed significantly reduced activation in BPD patients, including the ACC, superior temporal cortex, and amygdala (38). The insula also has an efferent connection to the inferior frontal gyrus, which showed greater activation in BPD patients, and both afferent and efferent projections to regions of the PFC that had significantly reduced activity in BPD patients (38). Given its extensive interconnections with several neural regions responsible for the subjective representation and regulation of emotion, the insula might play a crucial role in modulating negative emotions in patients with this illness. Increased activation within the insula itself might reflect a more intense subjective experience of negative emotion in these patients, and through its connections with anterior brain regions, it might be involved in modulating the efficiency of regulatory processes involved in the “top-down” control of emotion.

The subgenual ACC (BA 25) showed the most robust reduction in activity for BPD patients relative to control subjects. Indeed, this was the only area implicated in both study-reported between-subjects contrasts and independent subtraction ALE analyses on the basis of within-subjects comparisons of negative—neutral task conditions. The subgenual ACC is thought to be a key component of a neural network that—along with the amygdala, superior temporal cortex, and mid- and posterior cingulate cortex and other regions—is involved in the evaluative, expressive, and experiential aspects of emotion (39). In particular, activity in the subgenual ACC corresponds closely with that observed in the amygdala under conditions of high emotional conflict, and activity in both regions is strongly linked to trait levels of negative emotionality, particularly anxiety (40). Therefore, reduced activation in the subgenual ACC and amygdala in BPD might signify a diminished capacity for the regulation of emotions, especially under conditions of high negative emotionality that might require cognitive control to reduce the subjectively experienced intensity of emotion (41).

Because BPD patients show significant gray matter volume decreases in the ACC (42,43), it will be important for future work to statistically account for partial volume averaging effects in this region to determine whether these patients indeed show signs of reduced hemodynamic activity in this area. Nevertheless, these findings are noteworthy, because this region is thought to play a critical role in the etiology of major depressive disorder (MDD). Mayberg et al. (44) have consistently associated hyperactivity in this
region during negative emotion processing tasks with MDD, partic-ularly treatment-resistant depression. Interestingly, BPD patients show less activity in the subgenual ACC as compared with healthy individuals, a pattern of activity that lies in stark contrast to findings of greater activity in this region for patients with MDD. These findings, therefore, could suggest that reduced activity in this region might represent a distinct neural marker for BPD that could be used to distinguish this illness from patients with mood disorders (and no personality disorder). Indeed, these distinguishing neural under-pinnings for BPD as compared with MDD might refute the notion that BPD could be better understood as a variant of a mood disorder rather than a bona fide and distinct psychiatric illness (45,46). Given that BPD is often comorbid with MDD, future research should directly contrast BPD patients with MDD versus MDD patients without a personality disorder to evaluate the specificity of these findings.

The PFC has been the focus of many studies of BPD, because of its identified role in effortful emotion regulation (47,48) and response inhibition (49,50) in this illness. We found bilaterally reduced activation within the dorsolateral PFC in BPD patients relative to control subjects associated with negative emotion processing. Although the dorsolateral PFC is better known for its role in working memory and executive functioning (51), it might also play an important role in emotion regulation by way of its interaction with the amygdala, possibly by way of effortful cognitive strategies to modulate emotional experiences (52). Attenuated activity in the dorsolateral PFC in BPD likely reflects a diminished capacity for cognitive control in the modulation of subjectively experienced negative emotion. Increased activity in the left inferior frontal gyrus for BPD patients might also suggest a disruption of front systems involved in cognitive control, because this region is commonly associated with response inhibition (53). Heightened activity in this cortical region for BPD during negative emotion processing could denote a deficiency in inhibitory mechanisms involved in the modulation of emotion. These results also support neurocognitive findings of dorsolateral PFC and inferior frontal cortex dysfunction in BPD such as on tests of decision-making, cognitive flexibility, and motor response control (54).

Taken together, the results of this study are consistent with the theory that BPD patients might show hyperarousal in response to negatively valenced emotional stimuli, which might be subserved, at least in part, by heightened activity in the insular cortex. This hyperarousal might interfere with attentional disengagement from emotionally salient stimuli via efferent projections from the insula to anterior brain regions (ACC, dorsolateral PFC) that show significantly reduced functional activation in BPD. The BPD patients might therefore show a diminished capacity to efficiently modulate the intensity of subjectively experienced negative emotions, perhaps as a result of aberrant reciprocal connections between the insula and PFC. This neural network might also underlie well-documented deficits in emotion perception in BPD, especially those involved in the recognition of facial expressions of anger and disgust that are particularly affected in this illness (55). The neural systems dysfunc-tions revealed in this study are also consistent with those subserv-ing the capacity for mental state attribution (56), which is thought to be disrupted in BPD (57), and could underlie interpersonal deficits in this illness. Another potentially important implication of these findings is that neurobiologically based deficiencies in the regulation of negative emotions in BPD might conceivably be ame-liorated by psychological treatments aimed at improving the “top-down” regulatory capacities of these patients (22,58).

Several limitations should be considered as they relate to the current meta-analysis. First, there are a number of methodological and statistical concerns relating to the use of ALE for coordinate-based meta-analysis of neuroimaging data (for a review, see Eickhoff et al. [59]). Many concerns related to the assessment of spatial association between experiments and correcting for family-wise error and cluster-level significance level are addressed in the most recent version of the GingerALE BrainMap application (version 2.1), which was employed in the current meta-analysis. Second, to address the issue of variability across individual studies in the tasks used to evaluate negative emotion processing in BPD, we decided to use a broad definition of “negative emotion” paradigms (i.e., passive viewing, script-driven imagery), so as to synthesize as many individual studies on this topic as possible while also maintaining a reasonably narrow assessment of negative emotionality. In so doing, we acknowledge that our evaluation of this construct accommodates multiple aspects of negative emotionality (e.g., visual and aural stimuli, images of faces and scenes) and different types of instructional sets for emotional stimuli (e.g., passive viewing, recognition of emotions) that could be associated with distinct neural responses and might be obscured by pooling individual studies. Nevertheless, the concordance of results across studies using these diverse paradigms and instructional sets is striking and will help guide future work in this area. This study might also have limited generalizability, given the restrictions of the study selection criteria. The experimental paradigms examined in this meta-analysis might also not be generalizable to the real-life stressors experienced by BPD patients, although there are preliminary findings based on more ecologically valid social stressors relevant to BPD that are consistent with these results (60). Third, we were unable to sepa-rately evaluate the dimensions of valence and arousal for the emo-tion paradigms, because most studies reported results collapsing across (negative) emotional valence rather than arousal. Fourth, there are other potentially important brain regions not identified in this meta-analysis that require greater attention, because they might underlie aspects of emotion dysregulation in BPD. For example, the ventromedial/orbitofrontal PFC typically shows decreased activation in neuroimaging studies of BPD patients across a variety of task conditions (12,48,61– 63) and might have abnormally re-duced connectivity with the amygdala in these patients (64). Ac-cordingly, future work should emphasize the complexity of the interactions among brain circuits subserving negative emotionality in BPD and confirm the results of the current study using multiple methods (e.g., structural and functional neuroimaging). Fifth, there was significant comorbidity of BPD and mood disorders in individ-ual studies, which might call into question the specificity of these findings to BPD. There were, however, several areas of brain activa-tion revealed in this study that diverged considerably from those typically seen in patients with mood disorders (e.g., lower activation in BA 25 as compared with MDD). It could be argued that the results of this study are perhaps more generalizable to the majority of BPD patients who show considerable diagnostic comorbidity, especially with mood disorders. Nevertheless, future work is needed to di-rectly evaluate the specificity of these findings for BPD as opposed to other related disorders (e.g., mood disorders, other personality disorders) and understand how trauma might contribute to the neural substrates underlying affective processing in BPD (18,19).

Finally, the limited number of studies in this area that used a con-sistent negative emotion paradigm restricted our capability to per-form moderator analyses of potentially important task and sample characteristics. Given the characteristics of the studies included in this meta-analysis, it would be prudent to consider these findings as more representative of younger (approximately 30 years old) women with moderate to severe BPD. Future work should deter-mine the extent to which these findings are applicable to men with
BPD and the typically younger first-presentation patients (65) who are less-impacted by confounds relating to psychotropic medication use and other course-of-illness factors. These limitations notwithstanding, the results of the current study provide the first quantitative synthesis of functional neuroimaging findings in BPD and suggest that a dysfunction of specific frontolimbic systems might underlie negative emotionality in this illness.

The authors report no biomedical financial interests or potential conflicts of interest.


