Exaggerated and Disconnected Insular-Amygdalar Blood Oxygenation Level-Dependent Response to Threat-Related Emotional Faces in Women with Intimate-Partner Violence Posttraumatic Stress Disorder

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Background: Intimate-partner violence (IPV) is one of the most common causes of posttraumatic stress disorder (PTSD) among women. PTSD neuroimaging studies have identified functional differences in the amygdala and anterior cingulate cortex (ACC)/medial prefrontal cortex during emotion processing. Recent investigations of the limbic sensory system and its associated neural substrate, the insular cortex, have demonstrated its importance for emotional awareness. This study examined the hypothesis that women with IPV-PTSD show a dysregulation of this limbic sensory system while processing threat-related emotional faces.

Methods: 12 women with IPV-PTSD and 12 nontraumatized comparison women underwent blood oxygenation level-dependent functional magnetic resonance imaging while completing an emotional face-matching task.

Results: IPV-PTSD subjects relative to comparison subjects displayed increased activation of the anterior insula and amygdala and decreased connectivity among the anterior insula, amygdala, and ACC while matching to fearful versus happy target faces. A similar pattern of activation differences was also observed for angry versus happy target faces. IPV-PTSD subjects relative to comparison subjects also displayed increased dorsal ACC/medial prefrontal cortex activation and decreased ventral ACC activation when matching to a male versus a female target, and the extent of increased dorsal ACC activation correlated positively with hyperarousal symptoms.

Conclusions: Women with IPV-PTSD display hyperactivity and disconnection among affective and limbic sensory systems while processing threat-related emotion. Furthermore, hyperactivity of cognitive-appraisal networks in IPV-PTSD may promote hypervigilant states of awareness through an exaggerated sensitivity to contextual cues, i.e., male gender, which relate to past trauma.

Key Words: Amygdala, anterior cingulate, anxiety, emotion, insula, posttraumatic stress

Intimate-partner violence (IPV) is a worldwide public health problem (1), and a recent study identified IPV as the prime predictor of posttraumatic stress disorder (PTSD) among women (2). PTSD neuroimaging studies (Table S1 in Supplement 1) have produced evidence indicating abnormal function of two brain regions while processing threat-related emotional faces: the amygdala and the anterior cingulate cortex/medial prefrontal cortex (ACC/mPFC). The amygdala processes the detection of salient perceptual stimuli and integration of secondary emotional responses, as demonstrated by its crucial role in the fear response and aversive conditioning (3,4). This neural structure is especially responsive to interpersonal signals of threat, such as fearful faces, and these stimuli have proven to be useful experimental probes of amygdala function in PTSD (5). The ACC/mPFC is involved in a diverse array of higher-order cognitive and affective functions (6). The ventral portion has been found to display hypoactive function in PTSD (7,8), often interpreted as evidence of emotional dysregulation (9). Currently, the amygdala and ACC/mPFC constitute the core PTSD neurocircuitry model of emotional dysfunction. However, the recent proposal of a neural system supporting interoception as well as evidence for the importance of interoceptive cues in the experience of emotion (10) suggests that a model of emotional dysfunction focused exclusively on the amygdala and ACC/mPFC may be incomplete.

Interoception is defined as the sense of the internal body state and includes a range of sensations such as pain, temperature, itch, tickle, and sensual touch. Taken together, these sensations provide an integrated sense of the body’s physiological condition (11). The insular and anterior cingulate cortices have emerged as the primary neural substrates underlying interoceptive, i.e., limbic sensory processing and the subjective instantiation of feelings from the body, and they have also been demonstrated to be critically involved in processing emotion (12). Given the role of the insula in interoception and emotion, as well as evidence indicating abnormal anterior insular function in anxious samples (13,14), this region has been proposed to serve a crucial role in proneness to anxiety through generation of an exaggerated interoceptive prediction signal, i.e., anticipated aversive body state (15). Although contemporary neurobiological models of anxiety focus on the amygdala, the proposal of abnormalities in insular function as contributing to pathological anxiety complements this prevailing theory by providing a neuroanatomical...
substrate capable of influencing the two primary components of anxiety—sympathetic hyperarousal and worry—through its diverse reciprocal connections to sites involved in affective and executive function (12). While the amygdala is critically involved in the fear response and states of sympathetic arousal, experimental evidence implicates the insula in more “diffuse” anxiety responses, such as anticipation (16) and avoidance (17).

While prior studies have focused on amygdala and ACC/mPFC dysfunction as underlying emotional dysregulation in PTSD, fewer studies have examined the role of potentially abnormal interoceptive cues. Therefore, we used a widely published facial emotion-processing task (18), which is associated with robust and reliable activation of insula and amygdala (19,20), to examine the neural substrates that are important for processing interoceptive cues. Specifically, we sought to test these neural substrates’ response to threat-related emotion, e.g., by contrasting fearful relative to happy or neutral faces, which has proven to be a useful comparison for eliciting limbic abnormalities in PTSD (21,22). There is some evidence that neutral faces may not be processed as neutral by anxious populations (23,24). Therefore, we chose happy faces as the comparator condition, which have also been used elsewhere with PTSD subjects to isolate threat-related emotion (9,25).

Happy faces share similar interpersonal aspects with fearful faces but do not convey potential threat (26,27), which helps to delineate specific threat-related effects.

We also sought to examine two novel contrasts tailored to the IPV sample. Although all prior PTSD face-processing studies have used fearful faces to examine the limbic system, we hypothesized angry faces—another potential indicator of environmental threat (27)—might evoke limbic abnormalities due to the involvement of anger in the traumatic experience. Specifically, as perpetrators of IPV display more frequent and severe expressions of anger than nonviolent men and are prone to respond to anger by becoming aggressive (28), we predicted angry faces might serve to elicit limbic hyperactivity in this sample due to the experiential association of this facial expression with subsequent environmental threat from an intimate partner. To test this hypothesis, we examined the contrast of processing angry relative to happy target faces as a secondary probe of emotional threat. As both angry and fearful faces activate the amygdala (29) and the insula (30) in normal populations, we expected contrasts for threat-related emotion to primarily evoke increased activation in these regions for the IPV-PTSD sample.

Second, individuals with PTSD show increased sensitivity to potential trauma cues (31). We suspected that faces of male gender might evoke a general state of hypervigilance in female IPV-PTSD subjects, given the perpetration of trauma by a male intimate partner. It was hypothesized this hypervigilance would manifest as hypoactivation of the affective (ventral) subregion of ACC/mPFC and hyperactivation of the cognitive (dorsal) subregion of ACC/mPFC, consistent with the emerging understanding of this pattern of ACC differences as potentially reflecting the deployment of attentional resources toward salient stimuli in the presence of activated arousal networks (36,37).

Methods and Materials

Subjects

Twelve nontreatment-seeking women (n = 12) exposed to IPV and 12 comparison subjects participated in blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging. Intimate-partner violence trauma was operationalized as physical and/or sexual abuse by a romantic partner occurring within 5 years of study recruitment and having ended by at least 1 month before recruitment (mean number of years of abuse = 5.71, SD = 7.10, range = .5–25.5). All women in the IPV-PTSD group met full DSM-IV criteria for PTSD due to IPV, verified through the Clinician-Administered PTSD Scale (38) and the Structured Clinical Interview for DSM-IV (39). Comparison subjects had never experienced a criterion A traumatic event. Exclusionary criteria for both groups included: 1) substance abuse in the past year; 2) history of ≥2 years of alcohol abuse; 3) use of psychotropic medications in the past 4 weeks (or fluoxetine in the past 6 weeks); and 4) irremovable ferromagnetic bodily material, pregnancy, claustrophobia, bipolar disorder, or schizophrenia. Intimate-partner violence-PTSD subjects with comorbid mood/anxiety disorders were included as long as PTSD was judged to be the clinically predominant disorder. Written informed consent was obtained from all subjects, and the study protocol was approved by the University of California-San Diego Human Research Protections Program and the Veterans Affairs San Diego Healthcare System Research and Development Office. Groups were matched on demographic variables, except years of education, for which the IPV-PTSD group was significantly lower (Table S2 in Supplement 1). Therefore, education was used as a covariate in all group comparisons.

Self-Report Psychological Measures


Task

See Figure S1 in Supplement 1 for a depiction of the task.

Image Acquisition

Data were collected during task completion using functional magnetic resonance imaging parameters sensitive to BOLD contrast on a 3.0T GE Signa EXCITE (GE Healthcare, Milwaukee, Wisconsin) scanner (T2*-weighted echo planar imaging, repetition time = 2000 msec, echo time = 32 msec, field of view = 250 × 250 mm, 64 × 64 matrix, 30 2.6-mm axial slices with a 1.4-mm gap, 256 repetitions). A high-resolution T1-weighted image (172 sagittally acquired spoiled gradient recalled 1-mm thick slices, inversion time = 450 msec, repetition time = 8 msec, echo time = 4 msec, flip angle = 12°, field of view = 250 × 250 mm) was also collected from each participant for anatomical reference. Images were preprocessed by interpolating voxel time series data to correct for nonsimultaneous slice acquisition in each volume.

Behavioral/Psychological Measure Data Analysis

Participant data for self-report and behavioral measures were subjected to a split-plot, repeated-measures analysis of variance carried out in SPSS 15.0 (SPSS, Chicago, Illinois).
Image Processing/Analysis

Data were processed using the AFNI software suite (National Institute of Mental Health Scientific and Statistical Computing Core, Bethesda, Maryland) (40). Voxel time series data were co-registered to an intranuclear volume using a three-dimensional co-registration algorithm. Data were realigned to the anatomical space of each participant using the AFNI program 3dAllineate. Voxel time series data were corrected for artifact intensity spikes through fit to a smooth-curve function. Those time points with greater than 2 SD more voxel outliers than the subject’s mean were excluded from analysis (as determined by the AFNI function 3dToutcount). As small motion corrections in translational and rotational dimensions are nearly collinear, only rotational parameters (roll, pitch, and yaw) were used as nuisance regres-
sors for motion artifact. Two deconvolution analyses were con-
ducted—one for emotional threat-related contrasts and one for the gender contrast. For emotional threat, the orthogonal regres-
sors of interest were target trials of: 1) happy faces; 2) angry faces; 3) fearful faces; and 4) shapes. The outcome measures of interest were the linear contrasts of: 1) matching to a fearful versus happy target; and 2) matching to an angry versus happy target. For the gender contrast, the orthogonal regressors of interest were: 1) male target faces; 2) female target faces; and 3) shapes, for which the main outcome measure was the linear contrast of matching to a male versus a female target; this contrast controls for emotion by averaging across this factor in each gender condition. Regressors of interest were convolved with a modified gamma-variate function to account for delay and dispersion of the hemodynamic response. Baseline and linear drift variables were also entered into the regression model. The average voxelwise response magnitude was fit and estimated using AFNI 3dDeconvolve program. A Gaussian smoothing filter with a full-width at half maximum of 4 mm was applied to each participant’s normalized voxelwise percent signal changes with a full-width at half maximum of 4 mm was applied to each participant’s normalized voxelwise percent signal changes (PSCs) to account for individual variability in anatomical landmarks. Each subject’s PSCs were normalized to Talairach coordinates using AFNI’s built-in anatomical atlas (as specified by the Talairach Daemon, http://www.talairach.org/daemon.html) (41).

Whole-brain PSC data were entered into a one-sample voxel-
based t test to identify areas that activated significantly above the null for the effect of interest. An independent samples voxel-
based t test was used to identify areas significantly different between groups. A threshold adjustment based on Monte Carlo simulations (using AFNI program AlphaSim) was used to guard against false-positives in both the whole-brain and region-of-interest (ROI) analyses. A priori voxelwise probability of \( p < .05 \) with a 4-mm search radius and cluster size of 704 \( \mu \text{L} \) resulted in a posteriori probability of \( p < .05 \). In addition to a whole-brain analysis, a priori ROI analyses were conducted on brain regions implicated in emotion processing (bilateral insula, bilateral amygdala, and ventral/dorsal mPFC/ACC). Stereotactic coor-
dinates of these ROIs were based on standardized locations taken from the Talairach atlas (42). Protection against type I error for voxelwise a priori probability of \( p < .05 \) was obtained using cluster sizes of 192 \( \mu \text{L} \) for the amygdala, 320 \( \mu \text{L} \) for the insula, and 384 \( \mu \text{L} \) for the mPFC/ACC. Voxelwise activation values were extracted from areas of significant difference and subjected to further analysis in SPSS 15.0 for covariation of education.

Functional Connectivity Analyses

Functional connectivity analyses were conducted according to previously published methods (16). Data preprocessing in-
volved correcting echo planar signals for slice-dependent time shifts, Gaussian spatial smoothing with a 4-mm full-width at half maximum kernel, and bandwidth filtering (.009 < \( f < .08 \)). Normalization of images and censoring of outlier volumes were conducted as per activation analyses. In keeping with the experimental design of prior PTSD investigations of connectivity during emotion processing (21,22), individual time courses were extracted from each participant’s preprocessed echo planar time series for seed ROIs in the amygdala, ACC, and anterior insula showing task-dependent ROI activation for the fearful versus happy target contrast. The psychophysiological interaction of the time course for each seed ROI and the effects-coded contrast of fearful versus happy targets were calculated and entered into the deconvolution as the outcome variable of interest, along with task, movement, baseline, and linear drift regressors. An inde-
pendent-sample \( t \) test was used to examine group differences in voxelwise Fisher \( z \)-transformed correlation coefficients for the psychophysiological interaction. This connectivity difference map was then masked for ROI analysis in a priori regions of interest using the same technique (see above) to guard against false-positives. Voxelwise correlation coefficients were extracted from clusters of significant difference and were entered into SPSS 15.0 for co-variation of education.

Brain Activation Relationships with Self-Report Psychological Measures

Relationships between imaging data and written measures were assessed using voxelwise univariate regressions. Intimate-partner violence-PTSD participant subscales/total scores were regressed on individual activation maps. These scale-activation regression maps were masked for a priori ROIs, thresholded at \( p < .05 \), and clustered for minimum significant volume according to Monte Carlo simulations (as above). To identify IPV-PTSD functional differences associated with symptoms, these scale-activation regression maps were conjoined with the type I error-protected between-group ROI activation map and exam-
ined for significant overlap (as determined by Monte Carlo simulations on group effect clusters). Voxelwise activation values for areas of significant overlap were extracted and entered into SPSS 15.0 for confirmation of significance using Spearman’s \( r \), a nonparametric correlation that is robust to outliers. It should be noted that we did not restrict our experiment-wise \( \alpha \) level to .05 across all self-report measures when performing correlational analyses. As we used a conservative method for examining brain-behavioral relationships that did not employ circular analy-
ses—which can decrease voxelwise variability and inflate the magnitude of a correlation (43,44)—we felt that retaining a voxelwise \( \alpha \) level of .05 for each self-report measure scale would strike the most judicious balance between maximizing power and minimizing false-positives.

Results

Emotional Face-Matching Task Behavioral Data

There were no performance differences between IPV-PTSD subjects and comparison subjects as measured by response latency [repeated-measures analysis of variance covaried for education \( F_{\text{Group}} (1,20) = .771, p = .39 \); \( F_{\text{Group} \times \text{Emotion}} (2,19) = .952, p = .625 \); \( F_{\text{Group} \times \text{Gender}} (1,20) = .947, p = .304 \); \( F_{\text{Group} \times \text{Emotion} \times \text{Gender}} (2,19) = .853, p = .222 \)] or accuracy \( [F_{\text{Group}} (1,20) = 3.672, p = .07; F_{\text{Group} \times \text{Emotion}} (2,19) = .892, p = .339; F_{\text{Group} \times \text{Gender}} (1,20) = .938, p = .263; \) www.sobp.org/journal
\[ F_{\text{Group} \times \text{Emotion} \times \text{Gender}}(2, 19) = .844, p = .199; \text{Table S3 in Supplement 1}. \]

Brain Activation

See Tables S4, S5, S6, and S7 in Supplement 1 for results of task effect activation and connectivity analyses. All group differences reported below remained significant after covarying for education, and statistics are reported with education covaried out.

Threat-Related Emotion Contrast 1: Fearful Relative to Happy Target Faces. Between-group comparisons in a priori ROIs revealed significantly increased activation for the IPV-PTSD group in the left anterior insula and the right amygdala (Figure 1); whole-brain analysis also identified increased activation in brainstem, left middle frontal gyrus, and left precentral gyrus and decreased activation in the right middle temporal gyrus (MTG) (Table 1).

Threat-Related Emotion Contrast 2: Angry Relative to Happy Target Faces. Between-group comparisons in a priori ROIs revealed significantly increased activation for the IPV-PTSD group in the right mid insula, the left anterior insula, and the right amygdala (Figure 1, Table 2). Whole-brain analyses also showed these insular differences while revealing increased activation in areas such as the left precuneus, left cingulate gyrus, left MTG, and superior temporal gyrus, as well as decreased activation in the right middle frontal gyrus.

Gender Contrast: Male Relative to Female Target Faces. Between-group comparisons in a priori ROIs revealed significantly greater activation for the IPV-PTSD group in the bilateral dorsal ACC (dACC) and significantly reduced activation in the ventral ACC (vACC) and subgenual ACC (Figure 2, Table 3). Whole-brain analyses also showed these differences while demonstrating increased activation in the bilateral dorsomedial frontal gyri, left MTG, right supramarginal gyrus, right precuneus, and left precentral gyrus.

Activation Brain/Behavior Relationships

The conjunction of the group \( \times \) task effect map and the PTSD Checklist-Civilian Version (PCL-C) and Impact of Event Scale-Revised (IES-R) univariate regression maps in the IPV-PTSD group for matching to male relative to female faces revealed that hyperactivation in the dACC/medial frontal gyri was positively correlated with hyperarousal (PCL-C hyperarousal subscale: mean \( p = .695 \), mean \( p = .096 \); IES-R hyperarousal subscale: mean \( p = .586 \), mean \( p = .017 \); Figure S2 in Supplement 1). That is, greater hyperactivation in this region was associated with greater symptoms of hyperarousal. There were no significant regions of correlated activity identified with conjunctions of

![Angry Target vs. Happy Target](image1)

![Right Middle Insula](image2)

![Left Anterior Insula](image3)

![Fearful Target vs. Happy Target](image4)

![Left Anterior Insula](image5)

![Right Amygdala](image6)

**Figure 1.** Increased insular and amygdalar activation for intimate-partner violence-posttraumatic stress disorder vs. control subjects for matching to a fearful or angry versus happy target face. Graphs depict average voxelwise % signal changes for trials of each emotional expression vs. the sensorimotor baseline. Error bars depict \( \pm 1 \) standard error. IPV, intimate-partner violence; PTSD, posttraumatic stress disorder.
threat-related emotion contrasts or with conjunctions of remaining subscales of the PCL-C, IES-R, Childhood Trauma Questionnaire, Revised Conflict Tactics Scales, or Beck Depression Inventory; that is, there was no relationship between childhood trauma, past IPV trauma history/severity/type, or depression and patterns of group differences.

Functional Connectivity for Matching to a Fearful Relative to Happy Target Face

Between-group ROI analyses (Figure 3, Table 4) revealed significantly smaller correlation coefficients in the IPV-PTSD group in the left anterior insula with activity in the dACC seed ROI. Second, voxels in the left amygdala for the IPV-PTSD group were significantly less correlated with activity in the left anterior insula seed ROI. Third, the left anterior insula, left mid insula, right mid insula, and bilateral amygdalae showed significantly weaker correlations in the IPV-PTSD group with activity in a second, more dorsal left anterior insula seed ROI. Fourth, voxels in the left anterior insula in the IPV-PTSD group were more weakly correlated with activity in the amygdala seed ROI. Significantly stronger correlations with activity in the dACC seed ROI for the IPV-PTSD group were observed in the right posterior insula, and IPV-PTSD subgenual ACC activity was more strongly correlated with that in the right amygdala seed ROI.

Table 1. Areas of Significantly Increased or Decreased Activation for IPV-PTSD Versus Control Subjects for Matching to a Fearful Versus Happy Target Face

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Side</th>
<th>Anatomical Area</th>
<th>Size (µL)</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Voxelwise Statistics: Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>L</td>
<td>Insula (a)</td>
<td>448</td>
<td>−41.4</td>
<td>8.0</td>
<td>−4.6</td>
<td>6.035 (1.68)</td>
</tr>
<tr>
<td>ROI</td>
<td>R</td>
<td>Amygdala</td>
<td>320</td>
<td>28.4</td>
<td>−3.4</td>
<td>−15.3</td>
<td>5.277 (0.50)</td>
</tr>
<tr>
<td>WB</td>
<td>B</td>
<td>Brainstem</td>
<td>2304</td>
<td>−3.5</td>
<td>−34.4</td>
<td>−36.2</td>
<td>7.439 (3.81)</td>
</tr>
<tr>
<td>WB</td>
<td>L</td>
<td>Middle frontal gyrus</td>
<td>896</td>
<td>−44.7</td>
<td>16.9</td>
<td>29.9</td>
<td>7.250 (2.87)</td>
</tr>
<tr>
<td>WB</td>
<td>L</td>
<td>Precentral gyrus</td>
<td>896</td>
<td>−44.2</td>
<td>−7.1</td>
<td>37.9</td>
<td>6.698 (2.34)</td>
</tr>
<tr>
<td>WB</td>
<td>R</td>
<td>Middle temporal gyrus (−)</td>
<td>832</td>
<td>45.7</td>
<td>−71.0</td>
<td>14.2</td>
<td>8.307 (4.03)</td>
</tr>
</tbody>
</table>

Cluster coordinates and anatomical areas are for cluster center of mass as defined by Talairach stereotactic space. Negative (−) signs following anatomical area indicate reduced activation; descriptors for insula clusters do not reflect stereotactic distinctions but are estimates based upon the relative location of activation on the group map.

Table 2. Areas of Significantly Increased or Decreased Activation for IPV-PTSD Versus Control Subjects for Matching to an Angry Versus Happy Target Face

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Side</th>
<th>Anatomical Area</th>
<th>Size (µL)</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Voxelwise Statistics: Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>R</td>
<td>Insula (m)</td>
<td>704</td>
<td>41.2</td>
<td>4.5</td>
<td>12.8</td>
<td>6.410 (2.60)</td>
</tr>
<tr>
<td>ROI</td>
<td>L</td>
<td>Insula (a)</td>
<td>512</td>
<td>−42.1</td>
<td>10</td>
<td>−4</td>
<td>5.931 (1.49)</td>
</tr>
<tr>
<td>ROI</td>
<td>R</td>
<td>Amygdala</td>
<td>256</td>
<td>30</td>
<td>−4.5</td>
<td>14.5</td>
<td>5.702 (1.30)</td>
</tr>
<tr>
<td>WB</td>
<td>L</td>
<td>Precuneus</td>
<td>1344</td>
<td>−11.3</td>
<td>−51.4</td>
<td>43.6</td>
<td>8.234 (3.62)</td>
</tr>
<tr>
<td>WB</td>
<td>L</td>
<td>Cingulate gyrus</td>
<td>1088</td>
<td>−5.4</td>
<td>2.5</td>
<td>32.1</td>
<td>4.847 (5.55)</td>
</tr>
<tr>
<td>WB</td>
<td>L</td>
<td>Middle temporal gyrus</td>
<td>896</td>
<td>−56.1</td>
<td>−6.0</td>
<td>−7.7</td>
<td>5.663 (1.83)</td>
</tr>
<tr>
<td>WB</td>
<td>R</td>
<td>Insula (m)</td>
<td>832</td>
<td>42.6</td>
<td>4.0</td>
<td>12.7</td>
<td>5.717 (2.48)</td>
</tr>
<tr>
<td>WB</td>
<td>L</td>
<td>Precentral gyrus</td>
<td>832</td>
<td>−32.9</td>
<td>−9.7</td>
<td>34.1</td>
<td>8.648 (3.74)</td>
</tr>
<tr>
<td>WB</td>
<td>L</td>
<td>Superior temporal gyrus/insula</td>
<td>768</td>
<td>−45.2</td>
<td>10.6</td>
<td>−4.3</td>
<td>6.569 (1.63)</td>
</tr>
<tr>
<td>WB</td>
<td>L</td>
<td>Precentral gyrus</td>
<td>768</td>
<td>−25.1</td>
<td>−22.3</td>
<td>44.7</td>
<td>6.801 (2.22)</td>
</tr>
<tr>
<td>WB</td>
<td>L</td>
<td>Cerebellar tonsil</td>
<td>704</td>
<td>−35.5</td>
<td>−40.8</td>
<td>−31</td>
<td>4.895 (5.57)</td>
</tr>
<tr>
<td>WB</td>
<td>R</td>
<td>Middle frontal gyrus (−)</td>
<td>704</td>
<td>29.1</td>
<td>59.0</td>
<td>12.3</td>
<td>7.891 (3.29)</td>
</tr>
</tbody>
</table>

Cluster coordinates and anatomical areas are for cluster center of mass as defined by Talairach stereotactic space. Negative (−) signs following anatomical area indicate reduced activation; descriptors for insula clusters do not reflect stereotactic distinctions but are estimates based upon the relative location of activation on the group map.

Discussion

This investigation yielded three main findings. First, the anterior insula and amygdala of IPV-PTSD subjects were more active when individuals processed fearful or angry target faces. Second, at the same time, this increased activation occurred with attenuated connectivity among the dACC, anterior insula, and amygdalae during the processing of fearful faces. Third, the dACC/mPFC of IPV-PTSD subjects was more active when matching to a male versus a female target face, which was positively correlated with hyperarousal symptoms. Taken together, the limbic system activation pattern in IPV-PTSD individuals is consistent with exaggerated hyperarousal with exaggerated threat-related emotion contrasts or with conjunctions of remaining subscales of the PCL-C, IES-R, Childhood Trauma Questionnaire, Revised Conflict Tactics Scales, or Beck Depression Inventory; that is, there was no relationship between childhood trauma, past IPV trauma history/severity/type, or depression and patterns of group differences.

These results demonstrate that PTSD is characterized by hyperactivity of both the amygdala and anterior insula during the processing of threat-related emotion. Furthermore, the replication of amygdalar hyperactivity within an expanded face-processing paradigm reflects favorably on the external validity of the findings of prior PTSD imaging studies (Table S1 in Supplement 1). Fearful faces were originally utilized as nonspecific signals of threat-related emotion contrast with remaining subscales of the PCL-C, IES-R, Childhood Trauma Questionnaire, Revised Conflict Tactics Scales, or Beck Depression Inventory; that is, there was no relationship between childhood trauma, past IPV trauma history/severity/type, or depression and patterns of group differences.
threat to demonstrate the pervasive nature of PTSD limbic dysregulation (25). To our knowledge, this study presents the first evidence that angry faces may also serve as nonspecific signals of threat that are capable of eliciting limbic hyperactivity in IPV-PTSD subjects. It is possible that both fearful and angry faces signal the need to engage in self-preservative actions. Thus, increased activation of bottom-up limbic structures implicated in the detection of salient stimuli and representation of internal body states (29,30) in PTSD individuals may indicate an overgeneralization of exaggerated responding to certain emotional cues other than fear, per se. However, given the involvement of anger in IPV trauma, studies in other trauma samples are needed.

Table 3. Areas of Significantly Increased or Decreased Activation for IPV-PTSD Versus Control Subjects for Matching to a Male Versus Female Target Face

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Side</th>
<th>Anatomical Area</th>
<th>Size (µL)</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Voxelwise Statistics: Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>B</td>
<td>Ventral ACC (−)</td>
<td>1664</td>
<td>.1</td>
<td>35.1</td>
<td>−5.6</td>
<td>6.310 (2.14) .028 (.020)</td>
</tr>
<tr>
<td>ROI</td>
<td>B</td>
<td>Dorsal ACC</td>
<td>1088</td>
<td>1.6</td>
<td>31.4</td>
<td>22.2</td>
<td>9.091 (3.70) .014 (.015)</td>
</tr>
<tr>
<td>ROI</td>
<td>L</td>
<td>Subgenual ACC (−)</td>
<td>576</td>
<td>−4.4</td>
<td>16.9</td>
<td>−8.3</td>
<td>4.640 (1.18) .048 (.010)</td>
</tr>
<tr>
<td>WB</td>
<td>B</td>
<td>Dorsal ACC/medial frontal gyri</td>
<td>4992</td>
<td>3.5</td>
<td>43.7</td>
<td>22.7</td>
<td>8.350 (4.26) .020 (.028)</td>
</tr>
<tr>
<td>WB</td>
<td>L</td>
<td>Middle temporal gyrus</td>
<td>2432</td>
<td>−43.6</td>
<td>−60.7</td>
<td>19.7</td>
<td>6.192 (1.86) .030 (.025)</td>
</tr>
<tr>
<td>WB</td>
<td>B</td>
<td>Ventral ACC (−)</td>
<td>1664</td>
<td>.1</td>
<td>35.1</td>
<td>−5.6</td>
<td>6.443 (2.09) .026 (.016)</td>
</tr>
<tr>
<td>WB</td>
<td>R</td>
<td>Supramarginal gyrus</td>
<td>1536</td>
<td>39.9</td>
<td>−49.3</td>
<td>34.1</td>
<td>9.080 (2.67) .010 (.008)</td>
</tr>
<tr>
<td>WB</td>
<td>R</td>
<td>Precuneus</td>
<td>960</td>
<td>17.4</td>
<td>−62.6</td>
<td>34.2</td>
<td>7.255 (2.58) .022 (.019)</td>
</tr>
<tr>
<td>WB</td>
<td>L</td>
<td>Precentral gyrus</td>
<td>896</td>
<td>−48.1</td>
<td>−8.6</td>
<td>32.4</td>
<td>5.495 (1.59) .037 (.028)</td>
</tr>
</tbody>
</table>

Cluster coordinates and anatomical areas are for cluster center of mass as defined by Talairach stereotactic space. Negative (−) signs following anatomical area indicate a relative deactivation; descriptors for anterior cingulate cortex clusters do not reflect stereotactic distinctions but are estimates based upon the relative location of activation on the group map.

ACC, anterior cingulate cortex; B, bilateral; IPV, intimate-partner violence; L, left; PTSD, posttraumatic stress disorder; R, right; ROI, region of interest; WB, whole brain.

Voxelwise statistics are presented with education covaried out.

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to determine if this limbic hyperactivity reflects a more general threat-related functional abnormality or is more specific to the experience of IPV trauma.

We observed decreased vACC and increased dACC activation for matching to a male versus a female face, partially consistent with results of prior PTSD face-processing studies (9). While

Table 4. Significant Connectivity Differences for IPV-PTSD Versus Control Subjects for Matching to a Fearful Versus Happy Target Face

<table>
<thead>
<tr>
<th>Seed ROI</th>
<th>Side</th>
<th>Connection ROI</th>
<th>Size (µL)</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Voxelwise Statistics: Mean (SD)</th>
<th>p*</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal ACC</td>
<td>R</td>
<td>Insula (p)</td>
<td>384</td>
<td>38</td>
<td>-28.3</td>
<td>17.4</td>
<td>6.250 (1.94)</td>
<td>.016</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>Insula (a)</td>
<td>320</td>
<td>-41.9</td>
<td>11</td>
<td>12</td>
<td>9.064 (1.74)</td>
<td>.008</td>
<td>.005</td>
</tr>
<tr>
<td>Left Insula (a)</td>
<td>L</td>
<td>Amygdala (a)</td>
<td>448</td>
<td>-18.6</td>
<td>-5</td>
<td>-16.5</td>
<td>6.760 (3.07)</td>
<td>.035</td>
<td>.017</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>Insula (a)</td>
<td>448</td>
<td>-42.3</td>
<td>9.9</td>
<td>12.6</td>
<td>10.256 (3.06)</td>
<td>.007</td>
<td>.005</td>
</tr>
<tr>
<td>Left Insula (a)</td>
<td>L</td>
<td>Insula (a)</td>
<td>640</td>
<td>-35.5</td>
<td>13.9</td>
<td>-5.8</td>
<td>11.233 (5.21)</td>
<td>.013</td>
<td>.022</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>Insula (a/m)</td>
<td>640</td>
<td>-41.8</td>
<td>10.1</td>
<td>11.2</td>
<td>5.992 (2.03)</td>
<td>.035</td>
<td>.027</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>Insula (p)</td>
<td>512</td>
<td>41.4</td>
<td>-12.4</td>
<td>4.9</td>
<td>7.017 (3.03)</td>
<td>.025</td>
<td>.020</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>Amygdala (a)</td>
<td>320</td>
<td>26.7</td>
<td>-7.4</td>
<td>-15.2</td>
<td>5.170 (1.75)</td>
<td>.047</td>
<td>.030</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>Amygdala (m)</td>
<td>320</td>
<td>41.1</td>
<td>-14.1</td>
<td>-8</td>
<td>5.640 (.68)</td>
<td>.028</td>
<td>.008</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>L</td>
<td>Amygdala (a)</td>
<td>192</td>
<td>-24.7</td>
<td>-2.1</td>
<td>-12</td>
<td>6.016 (.80)</td>
<td>.024</td>
<td>.008</td>
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<tr>
<td></td>
<td>L</td>
<td>Insula (a/m)</td>
<td>1472</td>
<td>-36.1</td>
<td>-1.3</td>
<td>10.3</td>
<td>6.248 (3.26)</td>
<td>.040</td>
<td>.035</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Subgenual ACC</td>
<td>1088</td>
<td>-1.5</td>
<td>14.8</td>
<td>-8.9</td>
<td>6.616 (2.74)</td>
<td>.033</td>
<td>.037</td>
</tr>
</tbody>
</table>

Cluster coordinates and anatomical areas are for cluster center of mass as defined by Talairach stereotactic space. Negative (−) signs following anatomical area indicate reduced connectivity; descriptors for anterior cingulate cortex and insula clusters do not reflect stereotactic distinctions but are estimates based upon the relative location of activation on the group map. a, anterior; ACC, anterior cingulate cortex; B, bilateral; IPV, intimate-partner violence; L, left; m, middle; p, posterior; PTSD, posttraumatic stress disorder; R, right; ROI, region of interest; WB, whole brain.

*Voxelwise statistics are presented with education covaried out.
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