Laboratory Induced Aggression: A Positron Emission Tomography Study of Aggressive Individuals with Borderline Personality Disorder


**Background:** Borderline personality disorder (BPD) is often associated with symptoms of impulsive aggression, which poses a threat to patients themselves and to others. Preclinical studies show that orbital frontal cortex (OFC) plays a role in regulating impulsive aggression. Prior work has found OFC dysfunction in BPD.

**Methods:** We employed a task to provoke aggressive behavior, the Point Subtraction Aggression Paradigm (PSAP), which has never previously been used during functional brain imaging. Thirty-eight BPD patients with intermittent explosive disorder (BPD-IED) and 36 age-matched healthy control subjects (HCs) received 18fluoro-deoxyglucose positron emission tomography (18FDG-PET) on two occasions with a provocation and nonprovocation version of the PSAP. Mean relative glucose metabolism was measured throughout the cortex, and difference scores (provoked - nonprovoked) were calculated. A whole brain exploratory analysis for the double difference of BPD-IED - HC for provoked - nonprovoked was also conducted.

**Results:** BPD-IED patients were significantly more aggressive than HCs on the PSAP. BPD-IED patients also increased relative glucose metabolic rate (rGMR) in OFC and amygdala when provoked, while HCs decreased rGMR in these areas. However, HCs increased rGMR in anterior, medial, and dorsolateral prefrontal regions during provocation more than BPD-IED patients.

**Conclusions:** Patients responded aggressively and showed heightened rGMR in emotional brain areas, including amygdala and OFC, in response to provocation but not in more dorsal brain regions associated with cognitive control of aggression. In contrast, HCs increased rGMR in dorsal regions of PFC during aggression provocation, brain regions involved in top-down cognitive control of aggression, and, more broadly, of emotion.

**Key Words:** Brain imaging, emotion, Point Subtraction Aggression Paradigm, PSAP

Borderline personality disorder (BPD) is associated with elevated risk of violence (1). While symptoms of BPD traverse a number of domains, behavioral disinhibition, including aggression, is common (2,3). The present study used 18fluoro-deoxyglucose positron emission tomography (18FDG-PET) to examine brain activity changes during a behavioral aggression provocation task in healthy individuals and in BPD patients selected for serious impulsive aggression.

**Behavioral Disinhibition in BPD**

Borderline personality disorder brain imaging studies have shown disruption of the neural circuitry implicated in impulsive aggression, leading to the hypothesis that abnormal frontal inhibition of limbic regions may underlie BPD pathology. For example, anatomical magnetic resonance imaging (MRI) studies using manual tracing show volume reduction in BPD in frontal regions, including right anterior cingulate gyrus (ACG) (4), especially in gray matter volume (5), and decreased activity in ACG in response to a serotonergic probe (6,7). A recent study showed decreased gray matter volume in right orbital frontal cortex (OFC) in BPD adolescents (8). A resting 18FDG-PET study in BPD revealed an inverse correlation between lifetime aggression and OFC metabolism (9). Subsequent 18FDG-PET scans conducted in a resting state confirmed hypometabolism in BPD patients in OFC (10) and ACG (10,11). Together, these studies suggest that BPD patients have abnormal frontal modulation of limbic regions.

Functional imaging studies employing tasks to explore regional brain activity associated with specific emotional states have shown that in response to individualized abandonment scripts, BPD patients showed higher activation in anteromedial prefrontal cortex (PFC) compared with control subjects (12,13). Our recent functional magnetic resonance imaging (fMRI) study showed greater amygdala activation and attenuated activation in dorsal ACG and dorsal PFC to fearful in BPD compared with control subjects (14). Similarly, personality disorder patients with impulsive aggression show exaggerated amygdala reactivity and diminished OFC activation to angry faces (15). A recent BPD fMRI study showed a similar pattern of greater than normal activity in the amygdala and decreased ventromedial PFC activity during negative emotion provocation (16). Finally, correlational and connectivity studies have shown disruption of the PFC-amygdala network in BPD (17). Together, these studies provide...
support for a BPD model of diminished frontal inhibition of amygdala during emotion provocation.

Neuroanatomy of Violence

The brain regions shown to be dysfunctional in BPD have also been implicated more broadly in the control of aggression. In nonhuman primates, ablation of posterior OFC resulted in hyperactivity and aggression (18). Subsequent studies showed that after OFC lesions, rhesus monkeys exhibited decreased aggression (19). However, in high-dominance monkeys, increased aggression with loss of the dominance role was observed following OFC lesions (20). Very selective lesions of OFC in rhesus monkeys resulted in modest decreases in affiliative and increases in threat behaviors; however, other forms of aggression (e.g., intruder aggression) decreased (21). These studies point to a role for OFC in modulating aggression but also highlight the complexity of that role and the importance of social context to behavioral sequelae of OFC damage.

Human studies show that damage to anterior and medial OFC and ACG results in impulsive (22) and aggressive behavior (23,24). While this suggests that OFC may have a role in constraining impulsivity (25), the role of OFC is complex and may increase or decrease the likelihood of aggressive outbursts as a function of social cues and context (26).

Resting functional imaging studies have shown decreased metabolism in medial cortex/OFC in murderers (27,28) and in perpetrators of domestic violence (29). Two functional imaging studies of anger induction showed activation of OFC in healthy men (30,31). The only brain imaging study of aggression provocation to date showed that healthy men deactivate OFC during imagined aggression (32).

The present study is the first to gather functional brain imaging data during aggression provocation in both healthy control subjects (HCs) and impulsive-aggressive BPD patients. An 18FDG-PET scan was obtained on two separate days with the Point Subtraction Aggression Paradigm (PSAP), a task in which subjects play a game for points (later translated into money) with a putative other player (33). On one scan day, the task involved an aggression provocation, while on the other scan day, no provocation was used. We chose to study a subset of BPD patients, selecting those with clinically significant impulsive aggression (meeting criteria for intermittent explosive disorder-revised [IED-R]) (34) to find a homogeneous group of subjects with aggressive symptoms. We hypothesized amygdala would be more activated by aggression provocation in the BPD-intem-ittent explosive disorder (IED) than the control group and that top-down control regions of PFC would be less active in the BPD-IED than the control group.

Methods and Materials

Subjects

Thirty-eight patients meeting DSM-IV criteria for BPD and IED-R (22 male subjects/16 female subjects, age: 30.5, SD = 8.5 years) and 36 HCs (18 male subjects/18 female subjects, age: 28.4, SD = 7.1 years) with no personal or first-degree family history of psychiatric disorders completed the study. There was no significant group difference in sex distribution (χ² = 1, n = 74) = .46, p = ns) or in mean age between groups (F(1,72) = 1.4, p = ns) and no group × sex interaction [F(1,72) = 1.3, p = ns]. Subjects were recruited through local newspaper advertisements and clinical referral. All subjects were medically healthy as assessed by history, physical examination, and standard labora-

<table>
<thead>
<tr>
<th>Table 1. Demographics/Clinal Information</th>
<th>Group</th>
<th>Healthy (n = 36)</th>
<th>BPD-IED (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (Years)</td>
<td>Men:  n = 18, 27.9 (6.0)</td>
<td>Men: n = 22, 31.7 (8.6)</td>
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<td></td>
<td>Women: n = 18, 28.9</td>
<td>Women: n = 16, 28.8 (8.3)</td>
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<td></td>
<td>Range: 19–55</td>
<td>Range: 18–48</td>
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<td>4 H, 6 AA, 5 C</td>
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<tr>
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<tr>
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<td>32 right-handed, 4 left-handed, 2 mixed</td>
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<tr>
<td>ALS</td>
<td>M: 4 (4)</td>
<td>1.7 (7.6)</td>
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<td></td>
<td>M: 3 (3)</td>
<td>4.7 (5.6)</td>
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<tr>
<td>BIS</td>
<td>M: 51.6 (24.8)</td>
<td>83.8 (34.6)</td>
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<td></td>
<td>F: 48.8 (25.9)</td>
<td>F: 65.3 (12.0)</td>
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<tr>
<td>t-BUSS</td>
<td>M: 41.3 (6.9)</td>
<td>76.6 (8.7)</td>
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<tr>
<td></td>
<td>F: 41.2 (7.8)</td>
<td>75.8 (9.8)</td>
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<tr>
<td>STAXI-Trait</td>
<td>M: 13.9 (3.3)</td>
<td>27.0 (6.9)</td>
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<td></td>
<td>F: 13.9 (3.1)</td>
<td>F: 13.9 (3.7)</td>
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<tr>
<td>OAS-M agg</td>
<td>M: 1.2 (2.9)</td>
<td>20.6 (17.6)</td>
<td></td>
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<tr>
<td></td>
<td>F: 1.8 (4.0)</td>
<td>19.0 (18.7)</td>
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<tr>
<td>OAS-M irr</td>
<td>M: 1.2 (1.1)</td>
<td>6.3 (2.4)</td>
<td></td>
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<tr>
<td></td>
<td>F: 1.4 (1.2)</td>
<td>15.9 (2.1)</td>
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<td></td>
<td>F: 1.1 (1.9)</td>
<td>F: 1.4 (2.3)</td>
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<td>Data shown as mean (SD). Race is self-identified race. No clinical measures showed a main effect of sex or a diagnosis by sex interaction that was significant. A, Asian; AA, African American; agg, OAS-M aggression subscale; ALS, Affective Lability Scale; BDI, Beck Depression Inventory; BIS, Barratt Impulsivity Scale; BPD, borderline personality disorder; C, Caucasian; H, Hispanic; IED, intermittent explosive disorder; irr, OAS-M irritability subscale; O, Other; OAS-M, Overt Aggression Scale-Modified; STAXI, State-Trait Anger Expression Inventory; sui, OAS-M suicidality subscale; t-BUSS, Composite of Buss-Durkee Hostility Inventory (BDHI) and Buss-Perry Aggression Questionnaire (BPAQ). p &lt; .001. p &lt; .01.</td>
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into the study, as a high rate of PTSD in BPD has been reported (37) (see Tables S1 and S2 in Supplement 1 for full diagnoses and medication histories.) We explored the effects of PTSD and MDD on outcome measures, as the same neural circuits implicated in BPD may also function abnormally in PTSD (38) and MDD (39). Intermittent explosive disorder-revised diagnosis was made with the Module for Intermittent Explosive Disorder-Revised (34) (IED-R; \( \kappa = .92 \)). We employed this research diagnosis because of limitations in the DSM-IV diagnosis of IED, including the absence of a requirement for functional impairment resulting from aggressive acts, the exclusion of subjects in whom the aggressive acts are not “better accounted for” by personality disorders, and because it does not count verbal aggression (40). The diagnosis of IED-R addresses these deficits, expanding the DSM-IV definition (34, 41). Subjects completed the Barratt Impulsivity Scale-II (BIS-II) (42), Affective Lability Scale (ALS) (43), Beck Depression Inventory (BDI) (44), State-Trait Anger Expression Inventory (STAXI) (45), and the Overt Aggression Scale-Beck Depression Inventory (BDI) (46) or the Buss-Perry Aggression Questionnaire (BPAQ—updated BDHI) (47); a composite score was calculated, using Z scores. Handedness was determined with the Edinburgh Handedness Inventory (48).

The Point Subtraction Aggression Paradigm

The PSAP is a validated method of provoking aggression in a laboratory setting through a computer game (33, 49). It measures a participant’s aggressive responses to the subtraction of “points” worth money that he/she accumulates during a 35-minute testing session (standard 25 minutes; modified to match the \(^{18}\)fluoro-deoxyglucose \(^{18}\)FDG-uptake period), where losses are blamed on the responding of a fictitious other person. Unbeknownst to the subject, however, the level of provocation is set by the investigator as a provocation-free-interval (PFI). In the present study, we used two levels of provocation. In the provoked task, the PFI (which can be triggered by the subject pressing the B or C buttons) was set at 62.5 seconds; in the nonprovoked condition, the PFI was set at infinity and so no provocations occurred throughout the session. The active task was set at a high level of provocation to ensure that both the control subjects and the patients were provoked; if the control subjects had not also been provoked to some extent, we may not have activated the relevant brain related to the control of aggression in healthy individuals. This level of provocation also best separated control subjects from patients in previously completed behavioral data (unpublished). A no-provocation condition was chosen as a control task to avoid aggression provocation, while controlling for the visual, motor, and cognitive processes required for the task.

Prior to each testing session, subjects were instructed that the goal of the session was to earn as many points as possible, the points would be exchanged for money, and this other participant (the aggressive response); and pressing button C to protect him/herself from point subtractions for a period. Pressing button B is used as the measure of aggression. Since the validity of the PSAP depends on the participant’s belief that he/she is playing with another person (49), the participant was asked questions about characteristics of the other participant after completing the task. Note that prior studies of the PSAP have employed multiple rounds, while we employed one round on each task day to match the uptake period for \(^{18}\)FDG (49).

On two separate occasions (1 to 4 weeks apart, provoked and nonprovoked counterbalanced for order), each participant received 5 mCi of \(^{18}\)FDG. The subject remained resting in a sound-attenuated, dimly lit room for the 35-minute tracer uptake period, playing the PSAP. Following uptake, subjects were positioned in the positron emission tomography (PET) scanner for a 45-minute data acquisition period. Positron emission tomography scans were carried out as described elsewhere (6, 17, 50–52) (GE2048 head-dedicated scanner (GE/Scanditronix, Stockholm, Sweden), resolution 4.5 mm in plane, 5.0 mm axially). Fifteen slices at 6.5-mm intervals were obtained in two sets to cover the entire brain. Positron emission tomography images were obtained in nanocuries/pixel and standardized as relative glucose metabolic rate (rGMR) by dividing each pixel by the mean value for the entire brain. Brain edges were visually traced on all MRI axial slices with intertracer reliability of .99.

Regions of Interest Approach

We assessed rGMR within 39 Brodmann areas (BAs) in each hemisphere by tracing coronal slices based on a digitized brain atlas with 33 coronal slice maps of BAs defined by microscopic examination, a technique detailed elsewhere (17, 51–56). To assess the effect of provocation on rGMR, the dependent measure for PET analyses on task effect was expressed as difference scores (provoked – nonprovoked) within each BA. Selected sets of BAs developed on a theoretical and anatomical basis were entered into an analysis of variance (ANOVA) (nested within regions, e.g., orbital: BA 11 × 12 × 47). Amygdala was hand-traced on coronal MRI sections as described previously (17, 57).

Statistical Method

Behavioral ratings were entered into an ANOVA with the dependent variable as B button presses and diagnosis, sex, and provocation condition as factors. Positron emission tomography results for the provoked – nonprovoked conditions were analyzed with mixed factorial ANOVA. For the ANOVAs, we report the multivariate \( F \) (Greenhouse-Geiser) from Statistica (StatSoft, Tulsa, Oklahoma, http://www.statsoft.com) to adjust probabilities for repeated-measure effects with more than two levels. Fisher’s least significant difference (LSD) tests were used to follow-up significant interaction effects with diagnostic group. We examined only the frontal, sensory areas and cingulate BAs with nested ANOVA. Analyses of variance with the dependent variable as rGMR (provoked – nonprovoked) with group, sex, order, brain region, nested BAs, hemisphere, and tissue type were conducted for frontal, sensory, and cingulate cortex. The same analyses were repeated for the nonprovocation condition. This approach, which provided tests of hypothesized group differences, helps minimize type I errors involved with \( t \) tests for each area, group contrast, and hemisphere. In a further effort, we only examined significant main effects for diagnostic group and

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interactions between diagnostic group and gray/white and hemisphere or within-region BA effects. To examine symptom correlates with rGMR, we used Pearson correlations, using Bonferroni correction for multiple comparisons.

### Statistical Probability Mapping

We conducted whole-brain statistical probability mapping to confirm our regions of interest (ROI) findings and to explore brain regions not included in the ROI analysis. Positron emission tomography preprocessing involved nonbrain removal with FSL brain extraction tool (BET, FMRIB Centre, Department of Clinical Neurology, University of Oxford, United Kingdom) (58), 12-parameter registration to the Montreal Neurological Institute (MNI, McGill University, Montreal, Canada) brain template with FSL FLIRT (FMRIB’s Linear Image Registration Tool) (59), spatial smoothing with a Gaussian smoothing kernel at 10 mm full width at half maximum (FWHM), and intensity normalization (each voxel divided by the average value in the whole brain between Talairach z = −5 mm to z = 61 mm). Image differences between the provoked and nonprovoked conditions were computed for each subject. Group t tests were performed on these difference images between patients and control subjects. Voxel-by-voxel statistical maps were generated with FSL (http://www.fmrib.ox.ac.uk/fsl) (60) thresholded at \( t = 1.67 \) (\( p < .05 \), one-tailed) for display.

### Results

#### Subjects

As expected, the BPD-IED group had significantly higher scores in affective lability, impulsivity, aggression, and trait anger. The Axis I and Axis II comorbidities are similar to those reported in the Collaborative Longitudinal Study of Personality Disorders study, although with slightly lower levels of comorbidity (61). We believe that this is because we excluded subjects with current MDD, currently medicated, or abusing drugs or alcohol.

#### Behavioral Data

Aggressive responding was expressed as retaliatory B button presses. A group (HC, BPD-IED) × sex (male [M], female [F]) × order (provoked-first, provoked-second) × condition (provoked, nonprovoked) ANOVA revealed a main effect for diagnosis on aggressive responding \( [F(1,67) = 6.83, p < .01] \), with BPD-IED patients responding more aggressively than control subjects, consistent with our hypothesis. We also found a main effect of task condition, with both groups responding more aggressively to provocation than nonprovocation, as expected \( [F(1,67) = 14.55, p < .001] \); however, we did not find a group by condition interaction (Figure 1). There was neither a significant group difference in total button presses \((A + B + C)\) for the provoked or nonprovoked condition nor a significant effect for sex or order. There were no significant correlations between aggressive responding (B button presses: provoked – nonprovoked) and clinical measures of anger or aggression in the HC or BPD-IED groups. However, state anger \( (r = .45, p < .05, \text{corrected for multiple comparisons}) \) correlated with B button presses during the nonprovoked condition in the patient group but not in the control group. See Table S3 in Supplement 1 for full behavioral results.

#### PET Results: Provocation Effect

**Prefrontal Cortex.** A group (HC, BPD-IED) × sex (M, F) × order (provoked-first, provoked-second) × region (anterior, medial, orbital, dorsolateral) × BA (3) × matter (gray, white) × hemisphere (right [R], left [L]) ANOVA was performed to examine group differences in rGMR for the provoked – nonprovoked condition within the anterior (BA 8 × 9 × 10), orbital (BA 11 × 12 × 47), medial (BA 32 × 25 × 24), and dorsolateral (BA 44 × 45 × 46) regions of frontal lobe. A significant group by frontal brain region interaction was detected \( [G-G: F = 5.57, \text{corrected } df = (2.4,165.8), \epsilon = .79, p < .05] \). Healthy control subjects showed significant decreases in rGMR in OFC; in contrast, BPD-IED patients showed increased rGMR in OFC. The opposite pattern was seen in anterior, medial, and dorsolateral PFC (post hoc t tests: BPD-IED > HC in OFC, \( p < .05 \) (Figure 2). There was no significant effect involving order or sex.
We conducted a group (HC, BPD-IED) and amygdala (amygdala divided as previously described [17]). In the OFC, there is a pattern of group differences in rGMR such that, in the nonprovoked condition, healthy control subjects show significantly higher rGMR than BPD-IED patients and the opposite is true in the provoked condition. Post hoc tests for group differences are not significant for either the provoked or nonprovoked condition in OFC. BPD, borderline personality disorder; IED, intermittent explosive disorder; OFC, orbital frontal cortex; rGMR, relative glucose metabolic rate.

To examine the contribution of the nonprovoked condition to the group differences in OFC found in response to provocation, a group (HC, BPD-IED) × sex (M, F) × BA (3) × matter (gray, white) × hemisphere (R, L) × condition (provoked, nonprovoked) ANOVA was performed for the orbital BAs. We found a significant group by provocation condition effect [G-G: F(1,70) = 5.73, p < .05], with differences most pronounced in the nonprovoked rather than the provoked condition, although post hoc t tests on the individual conditions did not reveal significant differences in this finding (Figure 3). An exploratory analysis comparing BPD-IED patients with past PTSD (n = 13, 4 of 13 current PTSD) compared with those without (n = 25) to examine the effect of PTSD on our outcome measures revealed no significant group difference between BPD-IED ± PTSD. Similarly, an exploratory analysis comparing BPD-IED patients with past MDD (n = 23, 8 of 23 also with past PTSD) compared with those without (n = 15, 5 of 15 with past PTSD) to examine the effect of past MDD on our outcome measures and found no significant group difference between BPD-IED ± past MDD.

**Cingulate Gyrus.** A group (HC, BPD-IED) × sex (M, F) × order (provoked-first, provoked-second) × sex (M, F) × BA (25 × 24 × 31 × 23 × 29) × matter (gray, white) × hemisphere (R, L) ANOVA showed no significant effect involving group in cingulate cortex. Similarly, there was no significant difference for the presence of comorbid PTSD or past MDD for cingulate cortex in response to provocation.

**Sensory Areas.** Since OFC appeared offline at baseline, we explored the effect of provocation on sensory brain regions, exploring whether sensory areas would be most active in BPD-IED at baseline. We included occipital regions, parietal regions, and amygdala (amygdala divided as previously described [17]). We conducted a group (HC, BPD-IED) × sex (M, F) × region (occipital, parietal, amygdala) × subregion (BA 17 × 18; BA 41 × 42; amygdala: top × bottom) × hemisphere (R, L) ANOVA on rGMR for provoked − nonprovoked scores. We found a significant group × region interaction [G-G: F = 4.45, corrected df = (1.4, 89.5), ε = .68, p < .05] with HC increasing rGMR in occipital and parietal regions more with aggression provocation but less in amygdala with provocation. Borderline personality disorder-IED patients showed the opposite pattern with significantly lower rGMR in occipital and parietal regions during provocation but significantly higher rGMR in the amygdala during the provoked compared with the nonprovoked condition (*post hoc tests, p < .05). BA, Brodmann area; BPD, borderline personality disorder; IED, intermittent explosive disorder; rGMR, relative glucose metabolic rate.

**Clinical Correlations with ROIs**

Correlations between the behavioral scores for aggressive behavior (B button presses: provoked − nonprovoked) and amygadala with provocation. Borderline personality disorder-IED patients showed the opposite pattern with significantly lower rGMR in occipital and parietal regions during provocation but significantly higher rGMR in amygdala (Figure 4). To examine the contribution of the nonprovoked condition, we did an ANOVA of sensory areas in the nonprovoked condition and found that in amygdala, like in OFC, the most robust group difference was in the nonprovoked condition (Figure 5). Occipital and parietal BAs did not show this robust difference in the nonprovoked condition.

**Figure 3.** In the OFC, there is a pattern of group differences in rGMR such that, in the nonprovoked condition, healthy control subjects show significantly higher rGMR than BPD-IED patients and the opposite is true in the provoked condition. Post hoc tests for group differences are not significant for either the provoked or nonprovoked condition in OFC. BPD, borderline personality disorder; IED, intermittent explosive disorder; OFC, orbital frontal cortex; rGMR, relative glucose metabolic rate.

**Figure 4.** In an analysis of occipital cortex (BA 17, 18), parietal cortex (BA 41, 42), and amygdala (top, bottom), BPD-IED patients showed significantly more rGMR in amygdala than control subjects, while control subjects showed significantly higher rGMR in the occipital cortex during the provoked compared with the nonprovoked condition (*post hoc tests, p < .05). BA, Brodmann area; BPD, borderline personality disorder; IED, intermittent explosive disorder; rGMR, relative glucose metabolic rate.

**Figure 5.** In the amygdala, collapsed across hemisphere, there is a trend level group by condition interaction with the BPD-IED group tending to show higher rGMR with provocation than control subjects. There is also a significant effect of condition in BPD-IEDs with the amygdala more active to provocation than nonprovocation (*post hoc tests, p < .05). Post hoc tests for group differences are not significant for either the provoked or nonprovoked condition in amygdala. BPD, borderline personality disorder; IED, intermittent explosive disorder; rGMR, relative glucose metabolic rate.
affective lability, impulsivity, aggression, and trait anger with rGMR in prefrontal brain regions for provoked – nonprovoked conditions showed in HC, rGMR correlated with aggressive responding in left (r = .50, p < .01) and right medial (r = .61, p < .001), left orbital (r = .39, p < .05), and left dorsolateral (r = .36, p < .05) PFC. Left OFC correlated inversely with self-reported aggression (r = -.42, p < .05). These correlations were absent in the BPD-IED group. In BPD-IED, aggressive responding correlated with right anterior PFC (r = .34, p < .05). Significant group differences for the above correlations were seen in left (p < .01) and right (p < .001) medial OFC and left dorsolateral PFC (p < .05) with aggressive responding.

Nonprovocation Analysis

Prefrontal Cortex. Similar ANOVAs as were done for the provoked – nonprovoked conditions were also conducted on the nonprovoked condition. A group (HC, BPD-IED) × sex (M, F) × order × region (anterior, medial, orbital, dorsolateral) × BA (3) × matter (gray, white) × hemisphere (R, L) ANOVA was performed on rGMR for the nonprovoked condition. No significant main or interaction effect involving group was detected.

Cingulate. Similar to our findings in the provoked – nonprovoked condition, a group (HC, BPD-IED) × sex (M, F) × BA (25 × 24 × 31 × 23 × 29) × matter (gray, white) × hemisphere (R, L) ANOVA showed no significant effect involving group in the cingulate cortex.

Sensory Areas. A group (HC, BPD-IED) × sex (M, F) × region (occipital, parietal, amygdala) × subregion (BA 17 × 18; BA 41 × 42; amygdala: top × bottom) × hemisphere (R, L) ANOVA on nonprovoked rGMR showed no significant interaction involving group.

Of note, there was neither a main effect of sex nor any interaction involving sex that was significant for any of the ROI analyses, neither for the effect of provocation nor in the nonprovoked condition.

Statistical Probability Mapping

Figure 6 shows a whole-brain map for the double difference of BPD-IED – HC for provoked – nonprovoked. Consistent with our ROI analysis, in BPD-IED, rGMR increased more with provocation in OFC (extending more dorsally than the BAs included in our ROI analysis [shown in red → yellow in Figure 6]). In contrast, in HC, rGMR increased in regions of occipital and parietal cortex, as well as some areas of dorsolateral and dorsomedial PFC with provocation (shown in dark blue → pale blue in Figure 6).

Discussion

The current study examined OFC and amygdala responsiveness to aggression provocation. Previous resting PET studies suggested that aggression is associated with OFC underactivity (27,28,62). These studies have led to a simplified model that OFC “puts the brakes” on amygdala and that decreased OFC activity promotes aggression. The present study is consistent with this model, in that we show lower OFC activity in BPD-IED patients than HCs in the nonprovoked condition, but extends the model by providing evidence that OFC has a more complex modulatory role on amygdala responsiveness (26).

In our study, BPD-IED patients showed a robust pattern of low amygdala and OFC activity in the nonprovoked condition with hyperresponsiveness of these regions during aggression provocation compared with control subjects. The only previous study explicitly testing aggression provocation showed, as we have, that healthy control subjects deactivate OFC in response to aggression provocation (32). That study also found that medial and dorsolateral PFC were activated during the explicit cognitive control of aggression. Anecdotally, our patients report becoming easily angered, especially in response to interpersonal slights. They describe feeling overwhelmed by anger, with no access to controlling their responses or considering the consequences of not controlling them. Our study provides a possible functional imaging correlate of that experience, with increased rGMR in amygdala and OFC with provocation but not in the top-down control network seen in healthy individuals. Orbital frontal cortex appeared to be acting in isolation within PFC in patients but not in control subjects. Perhaps BPD-IED patients cannot activate the cognitive controls regions to keep them on task and are instead at the mercy of the limbic network of OFC and amygdala.

The PSAP is a social task in that the subject believes that he/she is playing with another individual. The rational choice is simply to avoid aggressive responding by pressing the A button, thereby gaining points/money. Pressing the B button is purely retaliative, providing no advantage to the subject. Unsurprisingly, control subjects largely avoided aggressive responses during nonprovocation; when provoked, they responded somewhat aggressively and activated top-down control brain regions, perhaps controlling that response. The correlation between the degree of activation of medial and dorsolateral PFC with aggressive responding could be viewed as supporting the notion that healthy subjects recruited top-down control regions to moderate their aggression. Borderline personality disorder-IED patients, in contrast, pressed the B button even when not attacked. Surpris-
ingly, we found no clinical correlations between aggressive responding and clinical measures of aggression, with the only correlation surviving Bonferroni correction between aggressive responding and anger in the BPD-IED group when not pro-

voked. This raises the possibility that aggressive behavior tapped into by this foreshortened version of the PSAP may be a nonpathological competitive aggression, and it is the presence of aggressive behavior when it is not appropriate (the nonprovocation condition) that might be most relevant for clinically problematic aggressive behavior.

Interestingly, we found no significant gender effect for any of our measures, including aggressive responding, rGMR in prefrontal brain regions, and cingulate and sensory regions, including amygdala. This seems surprising since men engage in more violent behaviors than women (63), although women are slightly more frequently physically aggressive in intimate relationships (64). Our findings of a robust effect of group on aggressive responding and on the neural circuitry activated by aggression provocation but no effect of sex suggest that the effect of the BPD-IED diagnosis may trump any gender effect on these outcome measures.

The strengths of our study include the novelty of our imaging task and the large sample of well-characterized currently medication-free BPD-IED patients. Also, our use of PET scanning rather than fMRI permitted us to examine OFC without susceptibility artifact. In addition, the PSAP task is particularly suited to PET imaging, since it involves a provocation of aggressive behavior during which the subjects move quite a bit; PET imaging, unlike fMRI, is not disrupted by subject motion, since the 18FDG uptake period precedes image acquisition. Our study does, however, have a number of limitations. First, we did not see a group by provocation condition interaction in our behav-

ioral result. Borderline personality disorder-IED patients responded more aggressively in both conditions. This raises the possibility that the underactivity of OFC and amygdala in BPD-IED patients compared with control subjects during nonprovocation arises from the fact that BPD-IED patients were already provoked to aggression and therefore showed a normal decrease in rGMR in OFC to aggression provocation. This seems unlikely since BPD-IED patients increased rGMR in these regions when provoked to even more aggression. Another possible interpretation is that since both groups heightened aggressive responding equally to provocation, perhaps we had reached a ceiling effect for provocation, with the BPD-IED group simply starting at a higher level. We did not measure subjective experience or physiological arousal during the game, which would have helped to illuminate our results. Finally, another limitation of our study is that our BPD-IED patients had a number of comorbid diagnoses, consistent with the rate reported by others (61). While we could not test for the effect of each of these diagnoses on our findings, we did find that BPD patients with past MDD or past or present PTSD did not differ significantly from those without such comorbidity.

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MSB is currently affiliated with the NeuroPET Center, San Diego, California.

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