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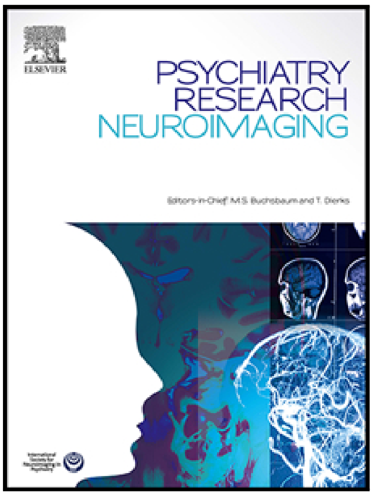

Neural Responses to Induced Emotion and Response to Social Threat in Intermittent Explosive Disorder

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PII: S0925-4927(21)00140-2
DOI: https://doi.org/10.1016/j.pscychresns.2021.111388
Reference: PSYN 111388

To appear in: *Psychiatry Research: Neuroimaging*

Received date: 23 February 2021
Revised date: 1 September 2021
Accepted date: 2 September 2021

Please cite this article as: Nicole Ogbuagu , Sarah Keedy , K. Luan Phan , Emil F. Coccaro , Neural Responses to Induced Emotion and Response to Social Threat in Intermittent Explosive Disorder, *Psychiatry Research: Neuroimaging* (2021), doi: https://doi.org/10.1016/j.pscychresns.2021.111388

Highlights.

Aggressive individuals have increased amygdala, and reduced orbitofrontal cortex in Functional Magnetic Resonance Imaging (fMRI) to social threat stimuli.

It is unknown if this is true for experienced emotion via the viewing of pleasant and unpleasant pictures.

We compared two fMRI task paradigms in 40 healthy controls and in 40 with Intermittent Explosive Disorder (IED).

Those with IED displayed increased fMRI Blood-Oxygen-Dependent Level responses to social threat (in amygdala), but not to evoked emotional, stimuli.

Abstract = 200
Text = 3,355
Tables = 4
Figures = 3

Neural Responses to Induced Emotion and Response to Social Threat in Intermittent Explosive Disorder

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ABSTRACT

Background: Individuals with intermittent explosive disorder (IED) are reported to exhibit amygdala (AMYG) hyper-activation to anger faces during functional magnetic resonance imaging (fMRI). However, it remains unknown if emotional experience is different in study participants with IED compared with healthy controls (HC). Thus, we examined the comparative effect of pleasant and unpleasant IAPS pictures in IED and HC individuals. Method: Eighty study participants (40 IED and 40 HC) underwent fMRI scanning while viewing blocks of angry and happy faces and while viewing blocks of pleasant and unpleasant pictures from the International Affective Picture System (IAPS). Results: Compared with HC participants, IED participants exhibited greater AMYG responses to angry, but not happy, faces; IED and HC participants, however, did not differ in AMYG responses to pleasant or unpleasant IAPS pictures. There were no group differences in Orbital-Frontal Cortical (OFC) responses to emotional faces or IAPS pictures other than a significantly higher OFC response pleasant, compared with unpleasant, IAPS pictures. Conclusion: These findings suggest that, compared with healthy individuals, those with IED have a hypersensitive amygdala to social-emotional threat but that this characteristic does not extend to neural responses related to the experience of emotion in the context of the paradigms tested.

Keywords: intermittent explosive disorder, aggression, fMRI, amygdala, OFC

1.0 Introduction

Intermittent Explosive Disorder (IED) is characterized by frequent impulsive aggressive outbursts (Coccaro, 2012; Kulper et. al., 2015). With a lifetime prevalence of about 3-5%, IED affects more individuals in the population than do many psychiatric disorders (Coccaro et. al., 2016). Compared to the general population, individuals with IED engage in more verbal and physical acts of aggression against others as well as damage to property (Kessler et. al., 2006; Kulper et. al., 2015). Not only are these acts of aggression distressing for the target of the aggression, they are also distressing for the aggressor. IED has been associated with significant impairment in psychosocial functioning and individuals with IED report increased occupational and interpersonal consequences to their outbursts of anger such as damaged friendships, job loss, and loss of romantic relationships (Rynar and Coccaro 2018; Kulper et. al., 2015).

A diminished ability to regulate emotions has, also, been found to be characteristic of IED. Individuals with IED experience negative emotions more intensely than the general public (Fettich et. al., 2015) and interpret ambiguous or benign social situations as more hostile and report them to be more anger-inducing (McCloskey et. al., 2016). This can be explained in part by the increased sensitivity to others' emotions that can be observed in those with IED (Falgren et. al., 2019). This oversensitivity to others' emotions plays a large role in the more intense experience of negative emotions in those with IED compared to healthy controls. In addition, those with IED also display increased alexithymia, or an inability to name their feelings, which, when paired with emotional dysregulation, makes it difficult to control aggression (Velotti et. al., 2016). Although evidence suggests dysfunction in global emotional regulation (Fettich et. al., 2015), there seems to be a deficit in regulating emotions revolving around anger specifically **(**Fahlgren et. al., 2019)**.** Those with IED display more anger rumination compared with healthy controls, meaning they tend to focus on thoughts or feelings of anger above other emotions (Fahlgren et al., 2019). Those with IED also show an increase in anger-directed affective lability, or the tendency to shift from one emotion to anger independent of a trigger (Fettich et. al., 2015).

Several studies have examined the neurological underpinnings of impulsive aggression, specifically as it relates to IED. Research has shown that individuals with IED, relative to controls, exhibit hyperactivation of the amygdala (AMYG) to anger faces (Coccaro et. al., 2016; McCloskey et. al., 2016). The amygdala is a well-studied brain structure found to play an essential role in emotion regulation and processing. The orbitofrontal cortex (OFC) is a related region that also has implications in emotional regulation with hypoactivation of the OFC to anger faces implicated in the pathology of impulsive aggression and IED (Coccaro et. al., 2011). In addition, a dysfunction in the OFC-AMYG circuit is linked to increased affective aggression and deficits in socioemotional processing and in rodent models of impulsive aggression and in individuals with IED (Coccaro et. al., 2006; Kuniishi et. al., 2017; Leclerc et. al., 2018).

While these neural and cognitive differences between those with IED and healthy controls are well documented, the neural differences represent only the social-emotional threat paradigm. Accordingly, there is no documented neural basis to explain the differences in emotional *experience* between healthy controls and individuals with IED. This distinction is important as there may be alternate neural mechanisms to explain these observed differences in emotional experience and the development of proper treatments will remain stalled if left understudied. To date, little work has been conducted on the emotional experience in IED using functional magnetic resonance imaging (fMRI). The present study attempts to fill in this gap by using International Affective Picture System (IAPS) images to induce emotion while subjects underwent an fMRI (Lang, Bradley, and Cuthbert, 1997).This set of stimuli in the form of images has been widely used in studies to elicit emotion in patients and healthy controls. Based on previous work, we hypothesized that IED study participants would display greater fMRI Blood-oxygen-level-dependent (BOLD) responses in the AMYG to: a) anger (but not happy) faces compared with healthy control participants and, b) unpleasant emotional IAPS stimuli compared with healthy control participants.

2.0 Methods

2.1 *Participants.* Participants consisted of 40 subjects meeting DSM-5 criteria for IED (American Psychiatric Association, 2013), and 40 healthy participants free of psychopathology. All were physically healthy, right-handed, and were recruited through media advertisement, seeking out individuals who reported psychosocial difficulty due to impulsive aggressive behavior or who were healthy. All participants gave written signed informed consent as approved by our Institutional Review Board (IRB). Individuals with bipolar disorder, schizophrenia, mental retardation, or current/lifetime alcohol or current substance use disorder were excluded. Medical health was documented by comprehensive medical history, exam, and urine screen for drugs of abuse.

2.2 <u>Diagnostic Assessment</u>. Syndromal psychiatric and personality disorder diagnoses were made by DSM-5 criteria (American Psychiatric Association, 2013). Research assessments were performed by individuals with masters/doctoral degrees in clinical psychology with inter-rater (kappa) reliability ranging from 0.79-0.93 (mean $\pm$ sd: 0.84 $\pm$ 0.05) across mood, anxiety, substance use, impulse control, and personality disorders. Final diagnoses were assigned by previously described best-estimate consensus procedures (Coccaro et al., 2012), utilizing information from: (a) Structured Clinical Interview for DSM Diagnoses (SCID; First et al., 1997), (b) Structured Interview for the Diagnosis of DSM Personality Disorder (SIDP; Pfohl et al., 1997); (c) Hare Psychopathy Checklist-Screening Version (PCL-SV; Hart et al., 2003), (d) clinical interview by a research psychiatrist; and, (e) review of all available clinical data. DSM-5 diagnoses for the subjects are listed in Table I. Most of the IED participants (73%) had a history of psychiatric treatment (38%) or of behavioral issues for which they should have received psychiatric evaluation and/or treatment (35%).

2.3 <u>Psychometric Measures</u>. Aggression was assessed with the Aggression score from the Life History of Aggression (LHA; Coccaro et al., 1997) assessment and with the Verbal and Physical Aggression scores from the Buss-Perry Aggression Questionnaire (BPAQ; Buss & Perry, 1992). The LHA assesses history of actual aggressive behavior and the BPAQ assesses aggressive tendencies as a personality trait. Impulsivity was assessed with the Life history of Impulsive Behavior (LHIB; Coccaro & Schmidt-Kaplan, 2012) and with the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995). The LHIB assesses history of actual impulsive behavior while the BIS-11 assesses impulsive tendencies as a personality trait. Sex, racial, and education data, collected by diagnostic assessors, reflected the self-identified characteristics of the subjects.

2.4 Preparation for Study. All participants were un-medicated. Alcohol breathalyzer and urine toxicology testing was performed at time of recruitment and on the day of the MRI scan and all subjects tested negative for alcohol and other drugs of abuse (opiates, cannabis, cocaine, hallucinogens, sedative-hypnotics). Subjects also reported no alcohol consumption in the three weeks prior to MR scanning.

2.5 Tasks and Materials

International Affective Picture System (IAPS) Emotion Task. fMRI data from this task have not been previously published. The emotional pictures task consisted of twelve 20-second alternating experimental/active (viewing 'PICTURE') and control (viewing gray-scale images; 'FIXATION') blocks, without any inter-stimulus interval, in each of four functional runs. The PICTURE blocks consisted of pictorial stimuli (5 per block) selected from the International Affective Pictures System (IAPS; Lang et al., 1997), and categorized as positive (e.g., pleasant), negative (e.g., unpleasant), and neutral based on normative ratings of valence. These emotional images have been shown to evoke acute and transient changes in subjective affective experience and arousal as well as peripheral and central indexes of emotional reactivity (Lane et al., 1997; Lang et al., 1993; Phan et al., 2002). The images within these categories were matched in color composition, general image complexity, and general content (presence of human faces). Positive, negative, and neutral picture blocks (2 blocks of each category per run) were counterbalanced within and across subjects, and no image was repeated. The FIXATION blocks (6 per run) consisted of blank, grey images (5 per block) with a centered fixation crosshair. Stimuli were presented through MR-compatible LCD goggles using PRESENTATION software (Neurobehavioral Systems, Albany, CA). In the PICTURE block, subjects were instructed to indicate by button press if the image block made them feel positive, negative, or neutral (i.e., rating of valence). In the FIXATION block, subjects were instructed to indicate by button press if the blank image was a dark, medium, or light shade of grey (rate shade), and to otherwise “rest, relax, and try not to think of anything.” The FIXATION blocks served as a simple visual-motor task to maintain the subjects’ attention but evoke little, if any, cognitive or emotional effort. After scanning participants viewed each of the 120 IAPS stimuli previously seen and subjectively rated each image on 9-point scales for valence (1=extremely unpleasant; 5=neutral; 9=extremely pleasant), and arousal (1=not at all arousing; 5=moderately arousing; 9=extremely arousing).

Ekman Emotional Faces Task. fMRI data from this task have been previously published in 55 of the 80 subjects in this report (13 HC/12 IED from McCloskey et al., 2016; 18 HC/14 IED from Coccaro et al., 2016) and are included as a contrast for the IAPS Emotion Task. The stimuli consisted of grey scale images of human facial expressions from the standardized Ekman and Friesen set (Ekman & Friesen, 1976). Subjects viewed the photos in a series of 20-second blocks of 5 face photos for each expression type (Angry and Happy). Each face block consisted of 5 consecutive trials (without any inter-stimulus interval) of one emotion type, presented for 4s each. Participants were asked to identify the emotional valence (positive, negative, neutral) of the face by button-press. FACE blocks were interleaved with 20 second FIXATION blocks during which subjects saw fixation crosses on a gray background and were asked to rate the shading of the background (light, medium, dark) by button-response. Each emotion expression type was presented once per run (4 total runs), and the block order was pseudorandom across runs and subjects.

2.6 Functional MRI Data Acquisition. Imaging was performed with Blood Oxygen Level Dependent (BOLD)-sensitive whole-brain fMRI on a 3 Tesla GE Signa scanner (Milwaukee, WI) using a standard radiofrequency coil. To minimize susceptibility artifact, whole-brain functional scans were acquired using a T2*-weighted reverse spiral gradient-recall-echo (GRE) sequence (TE=25ms, TR=2000ms, 64x64, flip angle=77°, field of view=24cm, 30 contiguous 5mm axial slices, aligned with the AC-PC line). A high-resolution T1 scan was acquired to provide precise anatomical localization (3D-MPRAGE) and to rule out structural abnormalities. Head movement was minimized by using foam inserts placed around the head and neck within the head coil.

2.7 Functional MRI Data Analysis

Data from all 80 participants met criteria for high quality and scan stability with minimum motion correction (<3 mm displacement in any one direction) and were subsequently included in fMRI analyses. The first four volumes from each run were discarded to allow for T1 equilibration effects. Functional data were analyzed using SPM12 (Wellcome Department of Cognitive Neurology, London; www.fil.ion.ucl.ac.uk/spm). The time series was spatially realigned to correct for head motion, corrected for slice timing, warped to Montreal Neurologic Institute (MNI) space, resampled to 2x2x2mm voxels, and smoothed with a 6mm kernel. The general linear model was applied to the time series, convolved with the canonical hemodynamic response function and with a 128 s high-pass filter. Condition effects were modeled with box-car regressors representing the occurrence of each block type. For each participant, statistical parametric maps (SPMs) were produced from linear contrasts of each emotion type (Anger and Happy) relative to fixation. We used a fixation block rather than neutral faces as the comparison condition as recent data suggests ambiguous stimuli such as neutral faces are actually processed as negatively emotional stimuli (Davis et al, 2016).

To test hypotheses about AMYG and OFC, we used an atlas-based region of interest (ROI) analyses approach. For AMYG ROI, we used boundaries from the Harvard-Oxford Atlas; (http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html#ho), yielding masks comprised of 81 2mm^2 voxels (approximately 0.65 cm) on each side (left, right). For OFC, we used the Automated Anatomical Labeling Atlas (AAL; *Tzourio-Mazoyer et al., 2002)* combining superior frontal gyrus orbital and medial portions and middle frontal gyrus orbital portions (right and left separately), yielding masks comprised of 6176 2mm^2 voxels (approximately 49.4 cm). These AMYG and OFC masks were used to extract mean activation from each contrast map (emotion vs. fixation) for subsequent group analyses.

2.8 Statistical Analysis

Statistical procedures were performed on extracted fMRI data using SPSS 22 and included parametric statistical procedures including t-test, ANCOVA / MANCOVA with Tukey for post-hoc testing, and Pearson correlation. The primary analysis involved repeated measures MANCOVAs with AMYG (and OFC) activation to Emotional Faces and IAPS pictures as dependent variables with and group (HC / IED) as the between subject factor and age, sex, ethnicity, and education as covariates. Given previous work, we hypothesized that IED study participants would display greater fMRI BOLD responses to: a) anger (but not happy) faces compared with healthy control participants and, b) unpleasant emotional IAPS stimuli compared with healthy control participants at a two-tailed α of 0.05. Means + standard deviation of the mean are reported unless otherwise stated.

3.0 Results

3.1 Characteristics of the Study Participants (Tables I and II). HC and IED study participants differed significantly in ethnicity and in socioeconomic score but not in age or in sex. IED participants were equally spread over the ethnicity groups whereas HC participants were predominantly white; IED participants had, also, completed less years of education compared with HC participants. For aggression and impulsivity variables, the IED group differed from HC as expected. Current and lifetime DSM-5 Syndromal diagnoses, and DSM-5 Personality Disorder diagnoses for the IED group are listed in Table II.

3.2 Behavioral Results to Ekman Emotional Faces and to IAPS Pictures (Table III). HC and IED participants did not differ significantly in their ability to correctly identify the facial expressions studied as positive, negative, or neutral in valence (MANCOVA: Wilks $\lambda = 0.91$, $F[3,72] = 2.49$, $p = 0.067$). In addition, HC and IED participants did not differ significantly in their emotional response to the IAPS pictures. Mean (+SD) valance scores for pleasant pictures were greater than both neutral and unpleasant pictures, which were significantly different from each other. Mean ($\pm$SD) arousal scores for pleasant and unpleasant pictures were both higher than that for Neutral pictures while the mean arousal score for unpleasant pictures was marginally greater than that for pleasant pictures ($p < 0.05$). Despite these differences, HC and IED participants did not differ in valence (MANCOVA: Wilks $\lambda = 0.99$, $F[3,74] = 0.33$, $p = 0.807$) or in arousal (MANCOVA: Wilks $\lambda = 0.99$, $F[3,72] = 0.23$, $p = 0.878$) in response to the IAPS pictures.

3.3 *Amygdala Activation to Ekman Emotional Faces and to IAPS Pictures*. Repeated MANCOVA for AMYG activations revealed a significant effect for group for Emotional Faces (Wilks' $\lambda = 0.94$, $F[1,74] = 4.70$, $p = 0.033$) but not for group for IAPS Pictures (Wilks' $\lambda = 0.97$, $F[1,74] = 2.30$, $p = 0.134$); figure 1. The difference for Emotional Faces was due to a significantly higher AMYG response to anger faces compared with HC participants.

3.4 *OFC Activation to Ekman Emotional Faces and to IAPS Pictures*. Repeated MANCOVA for OFC activations revealed no effect of group for Emotional Faces (Wilks' $\lambda = 1.00$, $F[1,74] = 0.00$, $p = 0.995$) but a significant effect of group for IAPS Pictures (Wilks' $\lambda = 0.92$, $F[1,74] = 6.05$, $p = 0.016$); figure 2. The difference for the OFC response to IAPS Pictures was due to a higher OFC response to Pleasant Pictures compared with Unpleasant Pictures in HC participants; IED participants displayed no differences in OFC activation with regard to Emotional Faces or IAPS Pictures.

3.5 *Relationship Between Amygdala and OFC Activations to Emotional Stimuli and Measures of Aggression and Impulsivity (Table V)*. Across all participants, composite aggression ($r = 0.29$, $p = 0.013$), but not composite impulsivity ($r = 0.14$, $p = 0.346$), scores correlated with the mean fMRI BOLD response to anger faces in AMYG. While no group differences were observed in the mean fMRI BOLD responses to emotional faces in the OFC, a significant inverse correlation was observed between mean fMRI BOLD response in OFC for happy faces ($\beta = -0.34$, $p = 0.004$), which remained statistically significant after accounting for the six correlations run for the OFC data ($p = 0.024$). Mean fMRI BOLD responses to anger faces in the AMYG, and to happy faces in the OFC, displayed no relationship with each other ($\beta = 0.01$, $n = 80$, $p = 0.942$). Multiple regression analysis, entering both these fMRI response variables (ANCOVA $F[6,79] = 5.80$ $p < 0.001$), revealed that both variables correlated with composite aggression score (AMYG/Anger: $\beta = 0.26$, $p = 0.010$; OFC / Happy: $\beta = -0.32$ $p = 0.003$); figure 3.

3.6 <u>Differential Activation to Ekman Emotional Faces and to IAPS Pictures in Other ROI Regions</u>. No differences were observed between HC and IED participants in cortical ROIs (anterior cingulate cortex, dorsal lateral prefrontal cortex, insular cortex, precuneus cortex, superior temporal gyrus, fusiform gyrus) or in subcortical ROI regions (hippocampus, caudate, globas pallidus, putamen, and thalamus) in response to Ekman Emotional Faces or to IAPS Pictures.

4.0 Discussion

We hypothesized that study participants with IED would exhibit an increased fMRI BOLD response in the amygdala only to anger faces in the Ekman Emotional Faces task and to Unpleasant images in the IAPS task. These results partially confirm this. Compared with healthy controls, individuals with IED showed a significantly greater AMYG fMRI BOLD response to anger faces which is in line with previous research (Coccaro et. al., 2007, McCloskey et. al., 2016) and explains the observed anomalies in social-emotional processing, such as heightened hostile attribution, in those with IED (Coccaro et al., 2009; 2016; 2017a,b).

Contrary to expectations, there were no differences in AMYG (or OFC) response to IAPS pictures between the groups. IAPS pictures did evoke differences in valance and arousal, as expected, but did not do so as a function of group. Thus, while both groups emotionally experienced the IAPS pictures in the same way, they did not differ in AMYG/OFC fMRI BOLD response. This suggests that AMYG/OFC responses in those with IED are not more sensitive to pleasant or unpleasant images which evoke corresponding emotions. It is possible that IAPS pictures are not as emotionally salient as anger faces, even when they represent negative stimuli (Heesink et. al., 2018). In addition, it is likely that the critical difference, here, is that angry faces represent the presence of a social threat rather than simply negatively valenced / arousing stimuli. This fits the current thinking about the role of social cognition in aggression which places the role of threat in a larger social context. For example, in the context of inflammation, AMYG fMRI BOLD responses are heighted only in response to social threat stimuli (e.g., emotional faces) not to non-social threat stimuli (e.g., snakes; Inagaki et al., 2012).

The results regarding the emotional faces task are similar to those previously reported because data from about two-thirds of these participants have been reported and were included, primarily, as a comparison for IAPS stimuli. That said, this larger sample allowed for more exploration regarding relationships between AMYG/OFC fMRI BOLD responses to anger faces and aggression and impulsivity. Specifically, we show a significant direct relationship between AMYG, and an inverse relationship between OFC, fMRI BOLD responses with composite aggression, though not impulsivity, scores. This is consistent with other observations that suggest that the relevant variance associated with impulsivity is due to its relationship with aggression.

In conclusion, individuals with IED, who show increased amygdala responses to social threat faces of anger, compared with controls, do not show this difference with respect to induced pleasant or unpleasant emotion in the context of IAPS pictures. Further research on the neural basis of emotional experience is needed to explain the differences in self-reported, subjective in emotional experience between individuals with IED and healthy controls (Fahlgren et al., 2019; Fettich et al., 2015). It may be useful to replicate this present study using other methods of emotion induction to paint a clearer picture of the dissimilar way healthy controls and individuals with IED experience emotion.

ACKNOWLEDGEMENTS

This work was supported by grants from the NIMH (RO1 MH66984, RO1 MH80108, and R01 MH104673) to Dr. Coccaro. In addition, this work was implemented, in part, with resources provided by the University of Chicago's Research Computing Center and by MRI Research Center.

DISCLOSURES

Dr. Coccaro reports being on the Scientific Advisory Board of Azevan Pharmaceuticals, Inc. and reports that he is a consultant to Avanir Pharmaceuticals, Inc. Drs. Keedy and Phan, and Ms. Ogbuagu, have nothing to declare.

TABLE 1

Demographic and Behavioral Data Among Groups

	HC (n = 40)	**IED (n = 40)**	**P**
Age (Years ± SD)[a]	32.0 ± 7.6	34.0 ± 8.5	= 0.117
Gender (Male / Female)[b]	17 / 23	15 / 25	= 0.820
Race (White / AA / Other)[b]	27 / 7 / 6	12 / 15 / 13	= 0.004
Education[b] (High School / College / Post-College	9 / 23 / 8	22 / 18 / 2	= 0.006
LHA Aggression Score[a]	4.8 ± 2.7	18.1 ± 4.2	< 0.001
BPA Aggression Score[a]	31.9 ± 12.2	47.4 ± 10.9	< 0.001
LHIB Impulsivity Score[a]	27.7 ± 19.2	49.6 ± 19.6	< 0.001
BIS Impulsivity Score[a]	54.6 ± 9.1	67.9 ± 9.3	< 0.001

[a] ANOVA, [b] Chi-Square test.

AA: African-American; LHA: Life History of Aggression; BPA: Buss-Perry Aggression;

LHIB: Life History of Impulsive Behavior; BIS: Barratt Impulsivity Scale

TABLE 2

Syndromal and Personality Disorder Diagnoses

for IED Group (n = 40)

Current Syndromal Disorders:	**Present**
Any Depressive Disorder	8 (20.0%)
Any Anxiety Disorder	13 (32.5%)
Any Substance Use Disorder	0 (0.0%)
Any Stress and Trauma Disorder	6 (15.0%)
Any Eating Disorder	2(5.0%)
Any Obsessive-Compulsive Disorder	0 (0.0%)
Any Somatoform Disorder	1 (2.5%)
Intermittent Explosive Disorder	34 (85.0%)
Non-IED Impulse Control Disorder	0 (0.0%)
Lifetime Syndromal Disorders:	
Any Depressive Disorder	27 (67.5%)
Any Anxiety Disorder	13 (32.5%)
Any Substance Use Disorder	3 (7.5%)
Any Stress and Trauma Disorder	9 (22.5%)
Any Eating Disorder	2 (5.0%)
Any Obsessive-Compulsive Disorder	0 (0.0%)
Any Somatoform Disorder	1 (2.5%)
Intermittent Explosive Disorder	40 (100.0%)
Non-IED Impulse Control Disorder	2 (5.0%)
Personality Disorders:	
Any Personality Disorder	36 (90.0%)
Personality Disorder Clusters:	
Cluster A (Odd)	4 (10.0%)
Cluster B (Dramatic)	15 (37.5%)
Cluster C (Anxious)	10 (25.0%)
Personality Disorder-Not Otherwise Specified	15 (37.5%)

TABLE 3

Behavioral Variables in Response to Emotional Faces and IAPS[a] Stimuli (Mean ± SD)

	ALL (n = 80)		**HC (n = 40)**	**IED (n = 40)**	**F[1,74][e] = / p =**
EMOTIONAL FACES					
Accuracy: *Mean (± SD)*					
Positive	0.91 ± 0.12[b]		0.93 ± 0.10	0.89 ± 0.13	F = 0.81; p = 0.371
Neutral	0.87 ± 0.11		0.90 ± 0.09	0.83 ± 0.12	F = 6.46; p = 0.013
Negative	0.79 ± 0.17		0.82 ± 0.18	0.76 ± 0.17	F = 0.55; p = 0.463
IAPS PICTURES					
Valance: Mean (± SD)					
Pleasant	6.95 ± 0.90[c]		7.01 ± 0.84	6.88 ± 0.96	F = 0.71; p = 0.402
Neutral	4.95 ± 0.55		4.97 ± 0.66	4.91 ± 0.42	F = 0.02; p = 0.898
Unpleasant	2.13 ± 0.97		2.12 ± 0.73	2.14 ± 1.17	F = 0.28; p = 0.600
Arousal: *Mean (± SD)*					
Pleasant	5.04 ± 1.66[d]		5.18 ± 1.60	4.90 ± 1.72	F = 0.25; p = 0.620
Neutral	2.31 ± 1.20		2.32 ± 1.13	2.30 ± 1.28	F = 0.10; p = 0.748
Unpleasant	5.56 ± 2.08		5.68 ± 2.06	5.44 ± 2.12	F = 0.14; p = 0.711

Notes: a) IAPS = International Affective Picture System.
b) Pleasant = Neutral > Unpleasant by repeated measures.
c) Pleasant > Neutral > Unpleasant by repeated measures.
d) Unpleasant > Pleasant > Neutral by repeated measures.
e) After MANCOVA (F[3,72]) with age, sex, ethnicity, education as covariates.

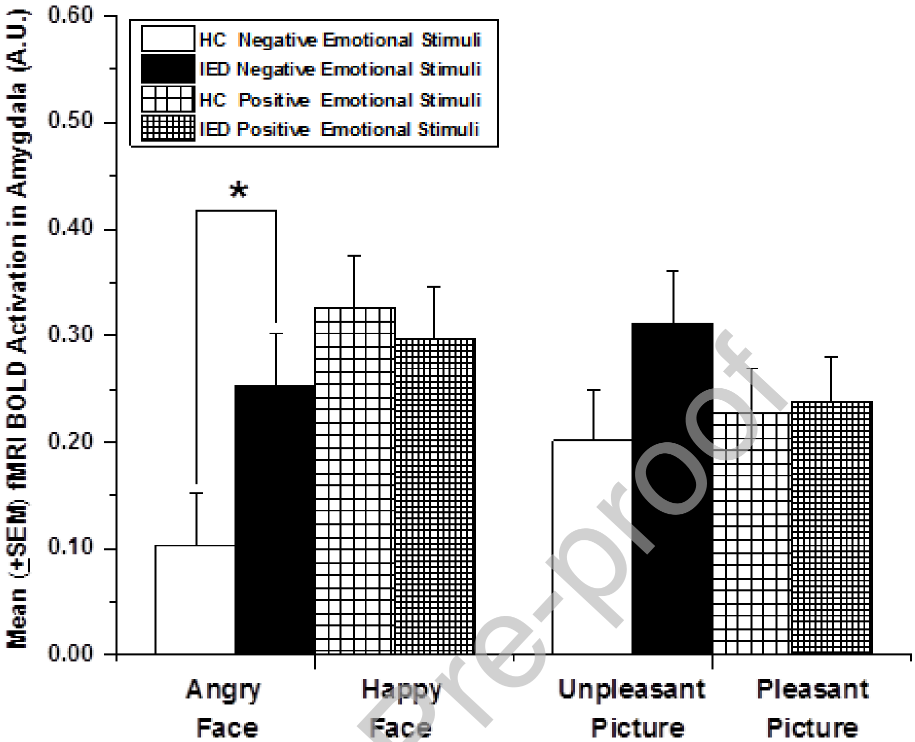
TABLE 4

Correlations with Composite Aggression Scores

fMRI BOLD Response	Composite Aggression Partial r (p) Amygdala (n = 80)	Composite Aggression Partial r (p) Orbitofrontal Cortex (n = 80)
Emotion Perception (Ekman Stimuli)		
Angry Face vs. Fixation	.28 (0.015)*	12 (0.306)
Happy Face vs. Fixation	.02 (0.888)	-.33 (0.004)*
Emotion Experience (IAPS Stimuli)		
Unpleasant vs. Fixation	-.07 (0.564)	-.09 (0.433)
Pleasant vs. Fixation	-.06 (0.620)	-.14 (0.231)

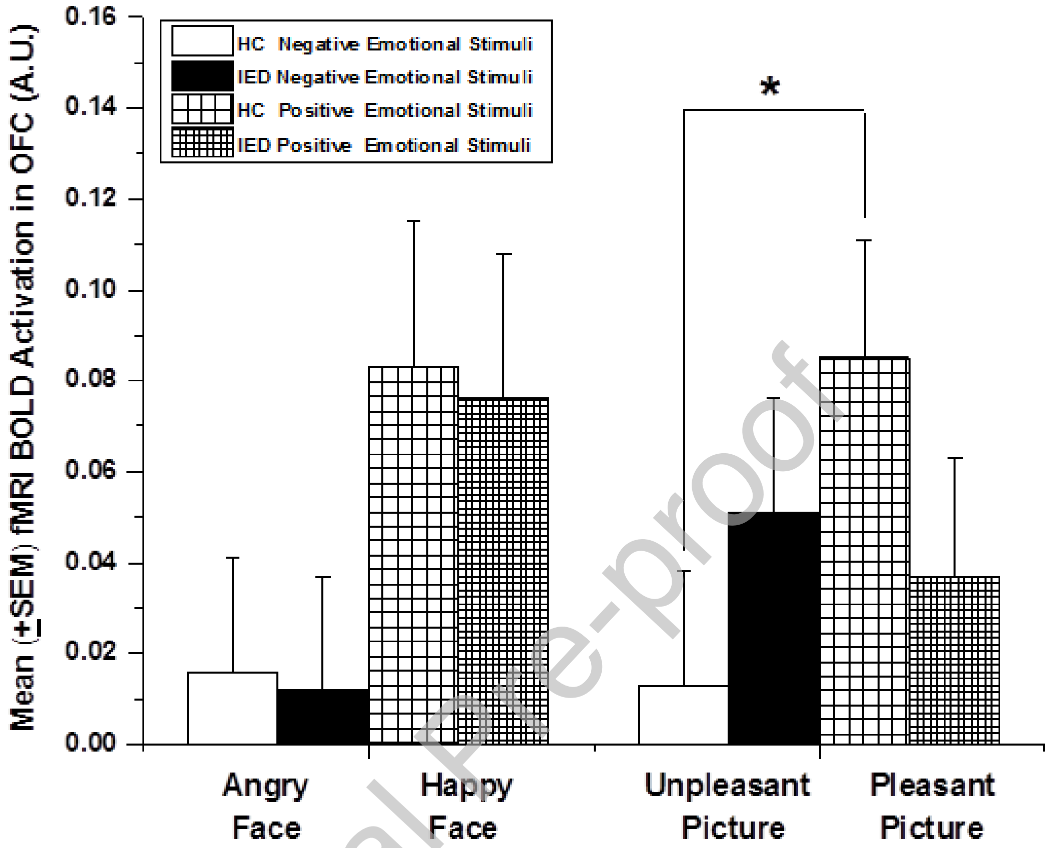
Notes. Covariates for partial correlation included age, sex, ethnicity, and education.

Figure 1.



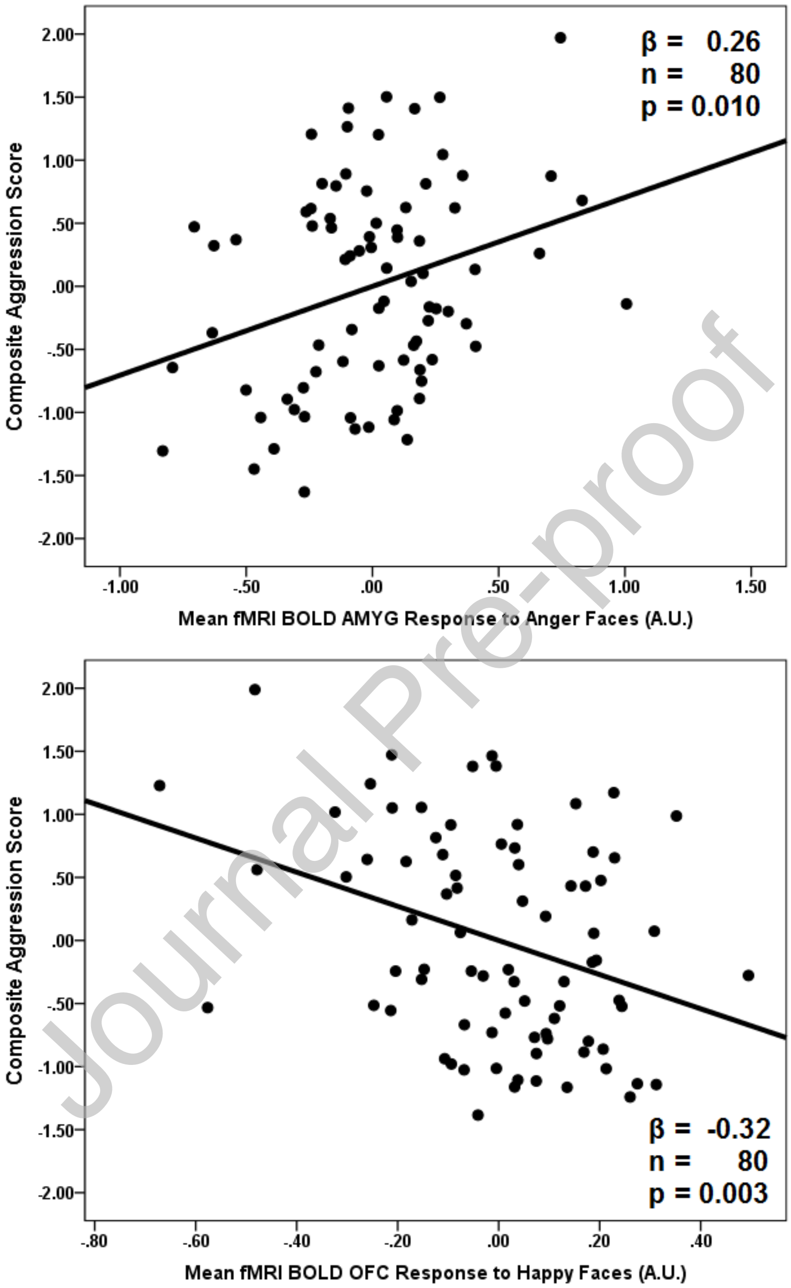
Mean (±SEM) fMRI BOLD Activation in Amygdala (A.U.)
0.60
0.50
0.40
0.30
0.20
0.10
0.00
HC Negative Emotional Stimuli
IED Negative Emotional Stimuli
HC Positive Emotional Stimuli
IED Positive Emotional Stimuli
*
Angry Face
Happy Face
Unpleasant Picture
Pleasant Picture

Figure 2.



Mean (+SEM) fMRI BOLD Activation in OFC (A.U.)
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
HC Negative Emotional Stimuli
IED Negative Emotional Stimuli
HC Positive Emotional Stimuli
IED Positive Emotional Stimuli
*
Angry Face
Happy Face
Unpleasant Picture
Pleasant Picture

Figure 3.


β = 0.26
n = 80
p = 0.010
Composite Aggression Score
2.00
1.50
1.00
.50
.00
-.50
-1.00
-1.50
-2.00
-1.00
-.50
.00
.50
1.00
1.50
Mean fMRI BOLD AMYG Response to Anger Faces (A.U.)
Composite Aggression Score
2.00
1.50
1.00
.50
.00
-.50
-1.00
-1.50
-2.00
β = -0.32
n = 80
p = 0.003
-.80
-.60
-.40
-.20
.00
.20
.40
Mean fMRI BOLD OFC Response to Happy Faces (A.U.)

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