

# Differential fMRI BOLD responses in amygdala in intermittent explosive disorder as a function of past Alcohol Use Disorder



Emil F. Coccaro<sup>a,\*</sup>, Sarah K. Keedy<sup>a</sup>, Stephanie M. Gorka<sup>b</sup>, Andrea C. King<sup>a</sup>, Jennifer R. Fanning<sup>a</sup>, Royce J. Lee<sup>a</sup>, K. Luan Phan<sup>b,c</sup>

<sup>a</sup> Department of Psychiatry and Behavioral Neuroscience, the University of Chicago, Chicago, IL, USA

<sup>b</sup> Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA

<sup>c</sup> Mental Health Service Line, Jesse Brown VA Medical Center, Chicago, IL, USA

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## ABSTRACT

**Background:** Individuals with intermittent explosive disorder (IED) were previously found to exhibit amygdala (AMYG) hyperactivation to anger faces during functional magnetic resonance imaging (fMRI). However, acute alcohol consumption, and/or life history of alcoholism, may blunt amygdala responses to negative emotional stimuli. Thus, we examined the influence of a past history of DSM-5 Alcohol Use Disorder (AUD) on the fMRI BOLD AMYG response to anger faces in IED.

**Method:** Forty-two IED participants, 18 with a past history of AUD (IED+AUD) and 24 without Past AUD (IED), and 32 healthy control (HC) participants, underwent fMRI scanning while viewing blocks of angry, fearful, and happy faces.

**Results:** Compared to HC and IED+AUD participants, IED subjects exhibited greater AMYG responses to angry, but not to fear or happy, faces in the left AMYG. There were no group differences in responses to anger, fear, or happy, faces in the OFC.

**Conclusion:** These findings suggest the possibility of a longstanding effect of AUD on AMYG response in IED to anger-related stimuli and highlight the possibility that history of AUD should be considered as an important factor in the interpretation of fMRI studies involving the AMYG response to negative emotional stimuli.

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## 1. Introduction

Impulsive aggressive behavior is the result of a multi-determined set of social, genetic, biological, and psychological factors (Coccaro et al., 2015). While the risk of impulsive aggression has long been associated with a reduction in central serotonergic function and resultant behavioral disinhibition, this factor is present at all times and cannot account for actual acts of impulsive aggression. Instead, factors present in the context of social interaction are most likely to trigger an impulsive aggressive act in vulnerable individuals. These factors are most likely represented by aberrant social-emotional information processing in which potentially threatening social cues lead to a state of anger directed at the other person in the social interaction and once the “threshold” for enacting an aggressive response is reached the individual engages in the aggressive act.

Impulsively aggressive individuals, such as those with

Intermittent Explosive Disorder (IED), have been shown to have aberrant social emotional information processing, specifically elevated hostile attribution and an elevated anger response to socially ambiguous stimuli (Coccaro et al., 2009), as well as an enhanced amygdala (AMYG) and reduced orbitofrontal cortex (OFC) responses to anger faces (Coccaro et al., 2007; McCloskey et al., 2016) compared with controls. This suggests that individuals with IED have aberrant behavioral and neural sensitivity to threatening, and to even potentially threatening, emotional stimuli compared with others without IED.

In addition to IED, the risk of impulsive aggression is elevated in individuals with history of Alcohol Use Disorder (AUD). Recently, we reported that the risk of current AUD in the general population is increased by more than five-fold in those with current IED (Coccaro et al., *In press*). Analysis of our clinical research sample extended this observation for lifetime IED and AUD as well (Coccaro et al., 2016). This substantial comorbidity between IED and AUD led us to ask if the neuronal correlates of aggression in comorbid IED+AUD cases would be similar, or dissimilar, to those in individuals with IED without AUD.

Review of the literature supports the hypothesis that AUD is

\* Corresponding author.

E-mail address: [ecoccaro@bsd.uchicago.edu](mailto:ecoccaro@bsd.uchicago.edu) (E.F. Coccaro).

associated with neural dysfunction in corticolimbic areas, including AMYG and OFC. Specifically, neuroimaging studies in individuals with AUD have reported alterations (e.g., reduced blood flow) in corticolimbic circuits (Durazzo et al., 2008; Hommer et al., 1997; Paul et al., 2008; Sullivan and Pfefferbaum, 2005; Volkow et al., 1992). Another study in long-time sober AUD subjects demonstrated reduced fMRI BOLD activation to emotional faces in AMYG compared to controls (Marinkovic et al., 2009). While it is not known how many of the subjects in these studies were aggressive, these findings run counter to what has been reported in impulsive aggressive subjects (Coccaro et al., 2007; McCloskey et al., 2016). On the other hand, those results are consistent with recent studies demonstrating that acute alcohol administration is associated with a reduction in fMRI BOLD response in AMYG but not OFC (Sripada et al., 2011) and to reduced coupling between AMYG and OFC when processing threatening faces, but not when processing happy faces (Gorka et al., 2013). Thus, it is possible that history of excessive alcohol consumption (AUD), observed in several individuals with IED, could be associated with a long standing reduction in brain activation patterns, especially in AMYG, and brain functional connectivity patterns, particularly between AMYG and OFC.

Accordingly, the current study compared the brain activation and connectivity in AMYG and OFC of participants in three groups: IED with AUD (IED+AUD), IED without AUD (IED), and healthy controls (HC) during a well-validated facial emotion processing task. Our primary hypothesis was that IED participants would display greater fMRI BOLD responses to anger faces in AMYG compared with IED+AUD and HC participants. We also examined activation of OFC, and connectivity between AMYG and OFC.

## 2. Methods

### 2.1. Participants

Participants consisted of 42 adult individuals meeting DSM-5 criteria for IED (American Psychiatric Association, 2013), and 32 healthy participants free of psychopathology. All were 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 alcohol or substance use disorder were excluded. Medical health was documented by comprehensive medical history, exam, and urine screen for drugs of abuse.

### 2.2. Diagnostic assessment

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 to 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 1. Most of the IED

participants (71%) had a history of psychiatric treatment (49%) or of behavioral issues for which they should have received psychiatric evaluation and/or treatment (22%).

### 2.3. Psychometric measures

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 and 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 and 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

Participants were unmedicated at time of recruitment and MRI scan. 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

The stimuli consisted of gray scale images of human facial expressions from the standardized Ekman and Friesen set (Ekman and Friesen, 1976). Subjects viewed the photos in a series of 20-second blocks of 5 face photos for each expression type (Angry, Fearful, and Happy). Each face block consisted of 5 consecutive trials (without any inter-stimulus interval) of one emotion type, presented for 4 s each. Participants were asked to identify the emotional valence (positive, negative, neutral) of the face by button-press. Face blocks were interleaved with 20 s “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 T 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=25 ms, TR=2000 ms, 64 × 64, flip angle=77°, field of view=24 cm, 30 contiguous 5 mm 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 74 participants met criteria for high quality and scan stability with minimum motion correction (< 3 mm

**Table 1**  
Demographic and behavioral data among groups.

	HC (n=32)	IED+AUD (n=18)	IED only (n=24)	Group differences
Age (years $\pm$ SD) <sup>a</sup>	29.9 $\pm$ 7.7	39.8 $\pm$ 7.7	33.0 $\pm$ 8.2	IED+AUD > HC=IED (Years)
Gender (M/F) <sup>b</sup>	8/24	14/4	10/14	IED=HC < IED+AUD (Males)
Race (White/Non-White) <sup>b</sup>	22/10	12/6	9/15	HC=IED+AUD > IED (Whites)
Education Level <sup>b</sup> (HS grad/college grad/post-college)	9/19/4	15/1/2	13/10/1	HC > IED > IED/AUD+ (College Grads)
LHA aggression score <sup>a</sup>	5.2 $\pm$ 3.1	19.4 $\pm$ 4.2	16.5 $\pm$ 3.6	IED+AUD=IED > HC
BPA aggression score <sup>a</sup>	16.0 $\pm$ 5.8	26.5 $\pm$ 5.5	21.4 $\pm$ 3.9	IED+AUD > IED > HC
LHIB impulsivity score <sup>a</sup>	31.5 $\pm$ 19.9	61.0 $\pm$ 12.9	43.0 $\pm$ 17.8	IED+AUD > IED=HC
BIS impulsivity score <sup>a</sup>	55.3 $\pm$ 6.6	73.6 $\pm$ 8.3	65.6 $\pm$ 8.6	IED+AUD > IED > HC

<sup>a</sup> ANOVA.

<sup>b</sup> Chi-square test.

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](http://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  $2 \times 2 \times 2$  mm voxels, and smoothed with a 6 mm 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, Fear, 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 2 mm<sup>2</sup> 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  $\times$  2 mm<sup>2</sup> voxels (approximately 49.4 cm). These AMYG and OFC masks were used to extract mean activation from each contrast map (emotional face vs. fixation) for subsequent group analyses. For connectivity analyses, consistent with our prior approaches, (McCloskey et al., 2016; Gorka et al., 2013) we used AMYG as seeds to construct connectivity maps (left and right AMYG yielded separate connectivity maps). We conducted generalized psychophysiological interaction (gPPI) analyses (McLaren et al., 2012), for connectivity during anger faces relative to fixation. We then extracted and averaged the resulting connectivity values from voxels within the OFC masks for each subject for analysis of group differences of AMYG-OFC connectivity.

## 2.8. Statistical analysis

Statistical procedures were performed on extracted fMRI data using SPSS 22 using parametric statistical procedures including *t*-test, ANCOVA / MANCOVA with Tukey for post-hoc testing, and Pearson correlation. Given previous work in the field, we hypothesized that past history of AUD (IED+AUD) would be associated with lower fMRI BOLD AMYG responses specifically to anger faces (and not to fearful or happy faces) compared with IED participants at a two-tailed  $\alpha$  of 0.05. We also hypothesized that AMYG responses would be lower among IED+AUD, compared

with HC, participants. Means  $\pm$  standard deviation of the mean are reported unless otherwise stated.

## 3. Results

### 3.1. Characteristics of the sample

Overall, HC, IED+AUD, and IED subjects differed significantly in mean age, proportion of males to females, in racial distribution, and in educational level (Table 1). Despite this, multiple regression analysis revealed no significant influence of these demographic variables on any of the fMRI BOLD AMYG, or OFC, responses to any of the emotional faces in this study (e.g., AMYG for anger faces:  $F[14,69]=0.19$ ,  $p=0.945$ ; OFC for anger faces:  $F[4,69]=0.36$ ,  $p=0.836$ ) and thus these variables were not included as covariates in subsequent analyses. For aggression and impulsivity variables, one or both IED groups differed from HC (Table 1). IED and IED+AUD subjects did not differ in comorbidity of other DSM-5 diagnoses except for a higher frequency of lifetime non-alcohol drug use disorder in the latter group ( $p=0.031$ ; four with past history of cocaine and cannabis use disorder, three with past history of cocaine use disorder only, and two with past history of cannabis use disorder only), a non-significant difference after accounting for multiple comparisons (Table 2). The time between the fMRI study and an active diagnosis of AUD, in the IED+AUD group, was  $11.8 \pm 9.9$  (range 1–25) years.

### 3.2. Behavioral and ROI neuroimaging results

#### 3.2.1. Behavioral results during the task

HC, IED, and IED+AUD participants did not differ in their ability to correctly identify the facial expressions studied as positive ( $F[2,71]=1.47$ ,  $p=0.238$ ), or negative ( $F[2,71]=1.57$ ,  $p=0.215$ ), in valence.

#### 3.2.2. Emotional faces and amygdala activation

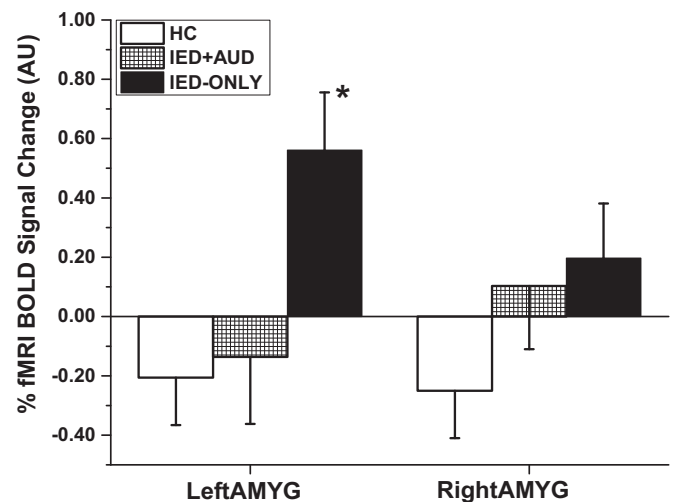
IED participants demonstrated a greater left AMYG response to anger ( $F[2,71]=4.89$ ,  $p=0.01$ ), but not fearful ( $F[2,71]=1.94$ ,  $p=0.152$ ) or happy ( $F[2,71]=1.12$ ,  $p=0.332$ ), faces compared with both IED+AUD and HC participants subjects (after MANOVA: Wilks  $\lambda=0.830$ ,  $F[6,138]=2.24$ ,  $p<0.05$ ); Fig. 1, left. There were no differences among all groups in right AMYG activation for all three emotional face types (MANOVA: Wilks  $\lambda=0.923$ ,  $F[6,138]=0.94$ ,  $p=0.464$ ), Fig. 1, right. Presence ( $n=8$ ), or absence ( $n=10$ ), of lifetime comorbidity of a non-alcohol drug use disorder in IED+AUD participants did not affect left AMYG responses to anger faces ( $t_{16}=0.21$ ,  $p=0.839$ ).

#### 3.2.3. Emotional faces and OFC

There were no differences in OFC activation among the

**Table 2**  
Syndromal and personality disorder diagnoses in the sample.

	IED + AUD (n = 18)	IED (n = 24)	P
<b>Current syndromal disorders:</b>			
Any depressive disorder	6 (27.3%)	5 (20.8%)	=0.734
Any anxiety disorder	5 (22.7%)	7 (29.2%)	=0.742
Any stress and trauma disorder	2 (9.1%)	5 (20.8%)	=0.418
Any eating disorder	1 ( 4.5%)	1 ( 4.2%)	=0.999
Any obsessive-compulsive disorder	0 ( 0.0%)	0 ( 0.0%)	=0.999
Any somatoform disorder	0 ( 0.0%)	1 ( 4.2%)	=0.999
Non-IED impulse control disorder	2 ( 9.1%)	0 ( 0.0%)	=0.233
<b>Lifetime Syndromal Disorders:</b>			
Any depressive disorder	17 (77.3%)	16 (66.7%)	=0.521
Any anxiety disorder	6 (27.3%)	8 (33.3%)	=0.754
Non-alcohol substance use disorder	9 (40.9%)	2 (8.3%)	=0.015
Any stress and trauma disorder	3 (13.6%)	8 (33.3%)	=0.171
Any eating disorder	2 (17.3%)	1 ( 4.2%)	=0.600
Any obsessive-compulsive disorder	1 ( 4.5%)	0 ( 0.0%)	=0.478
Any somatoform disorder	0 ( 0.0%)	1 ( 4.2%)	=0.999
Non-IED impulse control disorder	2 ( 9.1%)	1 ( 4.2%)	=0.600
<b>Personality Disorders:</b>			
Any personality disorder	21 (95.5%)	22 (91.7%)	=0.999
<b>Personality Disorder Clusters:</b>			
Cluster A (Odd)	5 (22.7%)	1 (4.2%)	=0.090
Cluster B (Dramatic)	13 (59.1%)	10 (40.7%)	=0.376
Cluster C (Anxious)	7 (31.8%)	7 (29.2%)	=0.999
PD-NOS	4 (18.2%)	8 (33.3%)	=0.321
PCL-SV callous-unemotional psychopathy	0 ( 0.0%)	0 ( 0.0%)	=0.999



**Fig. 1.** Extracted parameter estimates of activation for Angry (vs. fixation) facial expressions ( $\beta$  weights of BOLD Response, arbitrary units [AU]) from both left and right AMYG together, and separately, in the three groups. \*Signifies  $p < 0.05$  compared with IED+AUD and HC participants. HC=Healthy Control, IED+AUD=Intermittent Explosive Disorder with past history of Alcohol Use Disorder, IED=Intermittent Explosive Disorder without any history of AUD.

participants in response to anger, fearful, or happy faces in the left (MANOVA: Wilks  $\lambda=0.870$ ,  $F[6,138]=1.67$ ,  $p=0.134$ ) or right (after MANOVA: Wilks  $\lambda=0.865$ ,  $F[6,138]=1.67$ ,  $p=0.117$ ) OFC.

### 3.2.4. Functional connectivity

No group differences were observed in any of the gPPI analyses for functional connectivity between AMYG and OFC for angry faces relative to fixation.

### 3.2.5. Relationships with aggression and impulsivity

Across all participants, neither composite aggression ( $r=0.15$ ,  $p=0.213$ ), nor composite impulsivity ( $r=0.08$ ,  $p=0.514$ ) scores correlated with fMRI BOLD response to anger faces in left AMYG.

However, when only HC and IED participants were examined, composite aggression ( $r=0.32$ ,  $p=0.017$ ), but not composite impulsivity ( $r=0.15$ ,  $p=0.285$ ), scores correlated significantly with fMRI BOLD responses to anger faces in left AMYG. This was due to the correlation between fMRI BOLD responses to anger faces in left AMYG for LHA Aggression ( $r=0.33$ ,  $p=0.013$ ), but not BPAQ Aggression ( $r=0.19$ ,  $p=0.171$ ).

## 4. Discussion

In this study, we observed an enhanced activation to anger faces, specifically, in the left AMYG of IED participants compared with those of IED+AUD and HC participants. Despite left AMYG activation there were no group differences across groups in OFC to any of the emotional face types. Further, there were no group differences in connectivity between AMYG and OFC across emotional face types.

These findings are consistent with studies showing reduced AMYG responses to negative emotional stimuli in abstinent alcoholics, compared with healthy controls. In addition, these data are also consistent with recent observations that acute administration of alcohol, compared with placebo, reduces AMYG responses to negative emotional faces in social drinkers (Sripada et al., 2011). Most importantly, these data suggest that history of AUD, and alcohol usage in general, must be noted in neuroimaging studies of amygdala and cortic limbic circuits. Accordingly, we expected that individuals with past AUD would have lower amygdala responses to negative emotional stimuli compared with healthy controls (Marinkovic et al., 2009). However, given that the participants with AUD history in our study had concurrent IED, it is possible that a history of impulsive aggression affects this response to a level at or higher than what may be observed in healthy controls. In other words, IED and AUD may have independent and opposing effects on AMYG reactivity to angry stimuli.

It is also possible that alcohol use may have partly driven aggressive behavior in the IED+AUD participants. It is well known that acute administration of alcohol increases aggressive behavior (especially in those with an aggressive disposition; Giancola, 2002) and increases subjective stimulation and arousal (Loeber et al., 2010; Ratti et al., 2002). Alcohol administration also activates the ventral striatum (Gilman et al., 2008; King et al., 2010), an action that increases one's sensitivity to recognizing the emotion of anger (Calder et al., 2004). In animal studies, aggressive encounters are associated with increases in ventral striatum activity (Ferrari et al., 2003; Miczek et al., 2002; Redolat et al., 1991; Simon et al., 1989) and are blocked by D2 (but not D1) antagonists (Couppis et al., 2008). In a recent human study, ventral striatal activity was reported to increase along with increased aggressive responding during the influence of alcohol in a laboratory task of aggression (Gan et al., 2015).

Clinically, it is possible that individuals with IED "self-medicate" with alcohol to reduce stress-related dysphoria (including anger along with sadness and anxiety). If so, it is possible that alcohol consumption of sufficient severity to meet criteria for AUD may have modified AMYG responsivity to social threat, long term, in our IED+AUD participants (Marinkovic et al., 2009). Alternatively, it is possible that IED+AUD subjects are predisposed to reduced AMYG responding to social threat due to a greater likelihood of a family history of AUD in IED+AUD compared with IED participants. This possibility is consistent with a previous report that found reduced AMYG responding to social threat in young family members of alcoholics who were not alcoholics themselves (Glahn et al., 2007).

Observations from this study strengthen the positive association of AMYG responses to anger faces and higher LHA Aggression



(Coccaro et al., 2007). In this study, aggression scores were modestly higher in IED+AUD, compared with IED, but were still quite high in all IED subjects, as expected. There was no overall correlation between aggression or impulsivity scores and AMYG response to anger faces. While this appears to be at odds with previous findings, we note such correlations would be difficult to detect because IED+AUD subjects displayed AMYG responses to anger faces, similar to that of HC subjects, but had aggression and impulsivity scores similar to the IED participants. Instead, when correlations are examined without the IED+AUD participants, the expected correlations between aggression, but not impulsivity, and activation to anger faces in left AMYG emerge. This correlation was driven by life history of actual aggressive behavior and not be aggressiveness simply as a personality trait which did not correlate with brain activation. Second, the presence of the “callous-unemotional” form of psychopathy has been associated with reduced fMRI BOLD AMYG response to negative emotional stimuli (Dolan and Fullam, 2009; Harenski et al., 2010; Muller et al., 2003; Pujol et al., 2012; Rilling et al., 2007; White et al., 2012). However, no participant in this study met PCL-SV criteria (Hart et al., 2003) for psychopathy of the “callous-unemotional” type.

In some respects, these results differ from our previous reports (Coccaro et al., 2007; McCloskey et al., 2016). First, we used anger faces vs. fixation as our fMRI contrast, rather than anger faces vs. neutral faces. We chose fixation as our contrast because neutral faces are subject to variable interpretation as they are midway between extremes of emotional faces and IED subjects have been reported to label neutral faces as representing negative emotion (Best et al., 2002). Not surprisingly, it has now been shown that ambiguous/neutral faces lead to neural responses consistent with responses to negative emotion (Davis et al., 2016). Moreover, acute alcohol intoxication has been shown to enhance AMYG activation to neutral faces (Gilman et al., 2008). However, because we did not examine brain response to neutral faces specifically we cannot delineate AMYG and OFC responses to anger faces relative to neutral faces. Second, we found left, as opposed to right, AMYG as the structure accounting for the significant difference between the groups. This is in contrast to our previous reports noting significant differences between IED and HC participants as due to differences in activation to anger faces in right AMYG (Coccaro et al., 2007; McCloskey et al., 2016).

#### 4.1. Limitations

This study presents limitations that should be addressed. First, participants in this study were not optimally matched on the various demographic variables. In addition, participants with IED with, or without, past AUD differed in each of the demographic variables. While this could have influenced the imaging results, none of the demographic variables correlated with neuronal responses to any of the emotional faces and statistical control did not change any of these results. Second, participants were recruited from the community and not from psychiatric treatment centers. That said, most (71%) of the IED participants had a history of psychiatric treatment or of behavioral issues for which they should have received psychiatric evaluation and/or treatment, and therefore, may not be very different than those seen at treatment centers. Third, data regarding specific variables associated with past AUD (e.g., frequency or duration of alcohol use) were not collected. Thus, sub-analyses of the two IED groups regarding past alcohol use could not be reported. Fourth, our sample size of the IED sub-groups is relatively small and may have limited our power to detect AMYG and OFC group differences between IED+AUD and HC groups and group differences in AMYG–OFC connectivity. This is also true for comparisons looking at IED+AUD participants with and without non-alcohol use substance use disorders. In addition,

we also did not include an AUD-only group to allow assessment of pure history of AUD on our task. Finally, our task involved only anger, fearful and happy faces and thus we cannot infer how the current findings would relate and generalize to other emotional expressions (e.g., neutral, disgust, sad). These findings should be considered preliminary and require replication, and future studies are needed to address these important questions.

## 5. Conclusion

Enhanced fMRI BOLD response to anger faces in the left AMYG of IED participants without AUD was observed compared to study participants with IED with past AUD and in healthy controls. This was specific to anger, but not fearful or happy, emotional faces. These data suggest that history of AUD must be noted in neuroimaging studies of aggression, if not, also, in other studies involving the neuronal responsiveness of corticolimbic circuits.

## Contributions

Drs. Coccaro, Keedy, and Phan were involved in study design, analysis, interpretation, and manuscript writing. Drs. King, Gorka, Fanning, and Lee were involved in data interpretation and editing of the manuscript.

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