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

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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.

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

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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