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Amygdala hyperactivation to angry faces in intermittent explosive disorder

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ABSTRACT

Background: Individuals with intermittent explosive disorder (IED) were previously found to exhibit amygdala hyperactivation and relatively reduced orbital medial prefrontal cortex (OMPFC) activation to angry faces while performing an implicit emotion information processing task during functional magnetic resonance imaging (fMRI). This study examines the neural substrates associated with *explicit* encoding of facial emotions among individuals with IED.
Method: Twenty unmedicated IED subjects and twenty healthy, matched comparison subjects (HC) underwent fMRI while viewing blocks of angry, happy, and neutral faces and identifying the emotional valence of each face (positive, negative or neutral). We compared amygdala and OMPFC reactivity to faces between IED and HC subjects. We also examined the relationship between amygdala/OMPFC activation and aggression severity.
Results: Compared to controls, the IED group exhibited greater amygdala response to angry (vs. neutral) facial expressions. In contrast, IED and control groups did not differ in OMPFC activation to angry faces. Across subjects amygdala activation to angry faces was correlated with number of prior aggressive acts.
Conclusions: These findings extend previous evidence of amygdala dysfunction in response to the identification of an ecologically-valid social threat signal (processing angry faces) among individuals with IED, further substantiating a link between amygdala hyperactivity to social signals of direct threat and aggression.

1. Introduction

Aggressive behavior, a serious public health concern, is multi-determined by a complex set of interacting social, genetic, biological, and psychological factors (Berman et al., 2003) including poor socioemotional information processing. Aggressive individuals tend to interpret benign or ambiguous acts as hostile, perceive objectively hostile situations as more anger inducing, and react more aggressively to ambiguous situations (Matthews and Norris, 2002; Helfritz-Sinville and Stanford, 2014). Thus, aggressive individuals have deficits in how they interpret socioemotional information.

The amygdala and paralimbic prefrontal areas including (but not limited to) the orbital medial prefrontal cortex (OMPFC) play complementary roles in the regulation of aggression (Davidson et al., 2000). Human and primate studies show amygdala stimulation can facilitate aggression while amygdala ablation has the opposite effect (see Coccaro et al., 2011). In contrast, damage to the OMPFC increases aggressiveness (Anderson et al., 1999). Neuroimaging studies show functional abnormalities in the amygdala and prefrontal cortex among clinically aggressive groups such as spouse abusers (Lee et al., 2008), affective murderers (Raine et al., 1998), and subjects with borderline personality disorder and antisocial personality disorder (McCloskey et al., 2005). Recent findings also suggest abnormal structural connectivity between the

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amygdala and the orbitofrontal cortex in individuals with conduct disorder (Passamonti et al., 2012a).

The amygdala-prefrontal circuit also governs socioemotional information processing (Adolphs, 2002). Amygdala damage impairs the ability to recognize both basic (e.g. fear) and complex (e.g. flirtatiousness) social expressions (Adolphs et al., 2002), while OMPFC lesioning may reduce awareness of social cues (Mah et al., 2004), emotional facial expressions (Spikman et al., 2012), and one's emotional response (Angrilli et al., 2007). Imaging studies often show increased activation of the amygdala and OMPFC to emotional stimuli such as facial expressions (Phan et al., 2004), with the amygdala most often activating to fearful or threatening stimuli, which is thought to improve detection of such stimuli (Ohrmann et al., 2007). In violent men, both anatomical (i.e. decreased gray matter concentration) and functional (less differentiated activation pattern in response to threatening and neutral faces) abnormalities in the left dorsal amygdala may underlie the amygdala hyper-reactivity to social signals that characterize reactive aggression (Bobes et al., 2013). Furthermore, bilateral ventral amygdala volume was positively associated with motor impulsivity, while left dorsal amygdala volume was negatively associated with aggression in psychiatric patients (Gopal et al., 2013). The OMPFC is also responsive to threat and may be preferentially activated to facial expressions of anger (Nomura et al., 2004).

Few studies have examined the functional neuroanatomy of social information processing among affectively aggressive individuals. Subjects high on the reward drive scale of the Behavioral Approach System (which is associated with anger (Harmon-Jones, 2003)) show increased amygdala and decreased ventral anterior cingulate/ventromedial prefrontal activation to angry faces (Beaver et al., 2008). Among clinical populations, subjects with borderline personality disorder show OMPFC hypoactivity and amygdala hyperactivity during processing of emotionally negative stimuli (Donegan et al., 2003; Schmahl et al., 2004). Similarly, depressed patients with anger attacks demonstrated medial PFC hypoactivity and differential medial PFC-amygdala interactions in response to anger-inducing script imagery (Dougherty et al., 2004). However, for these subjects, when it existed, aggression was secondary to another disorder.

Intermittent Explosive Disorder (IED), a disorder of affective aggression (American Psychiatric Association, 2013), is prevalent in approximately 5% of the population (Kessler et al., 2006). Individuals with IED evidence many of the deficits found in dimensional studies of aggressive individuals, including poor facial emotion recognition (Best et al., 2002) and a hostile attribution bias (Coccaro et al., 2009a). Thus, IED represents a clinically relevant aggressive population with well-defined characteristics (Coccaro et al., 2014).

Earlier research (Coccaro et al., 2007) found that IED subjects showed amygdala hyperactivation and reduced OMPFC activation when viewing angry (but not other emotional) faces. Furthermore, control, subjects showed reciprocal (negative) functional connectivity between the amygdala and OMPFC; whereas IED subjects showed no functional connectivity. These findings, though informative, were based on a small sample (10 IED subjects and 10 controls), and therefore one of the aims of the present study was to validate and replicate these findings in a new and larger sample. Furthermore, Coccaro and colleagues (2007) used an implicit emotion identification task (gender identification). However, explicit emotion identification and processing may be important in targeting affective dysregulation in treatment for affective aggression for IED. Thus, the present study seeks to extend previous findings to explicit socioemotional information processing, which is associated with lower amygdala activation and increased medial PFC activation (Lieberman et al., 2007). Given that individuals with IED show hostile attribution biases when interpreting emotions (Coccaro et al., 2009a), understanding the exact nature of the deficit in emotion processing at the neural level can have important implications for psychosocial and pharmacological treatment approaches.

The current study compared the brain activation of 20 IED and 20 healthy control subjects during a well-validated facial emotion task in which subjects had to identify the emotional valence of each face presented. Our primary hypothesis was that patients with IED would have greater amygdala and less prefrontal (specifically OMPFC) activation to angry faces relative to controls. We also hypothesized that control subjects, but not IED patients, would show reciprocal functional connectivity between the amygdala and OMPFC.

2. Methods

2.1. Participants

Participants consisted of 20 subjects meeting DSM-V criteria for IED (APA, 2013) and 20 healthy control (HC) subjects. Subjects were excluded if they reported (a) current psychopharmacological treatment, (b) lifetime bipolar or psychotic disorder, (c) a traumatic head injury, or (d) a current major depressive episode or substance dependence. HC subjects were excluded if they reported any history of psychopathology. All DSM-5 disorders were evaluated using the Structured Clinical Interview for syndromal disorders (First et al., 1995) and the Structured Interview for the Diagnosis of Personality Disorders (Pfohl et al., 1995) as previously reported (Coccaro et al., 2012).

All subjects were right handed and had normal or corrected to normal vision. IED and HC groups were matched for gender (8 female, 12 male), race (12 Caucasian, 6 African American, 2 Asian) and age within 5 years (IED $M = 33.2$ years, HC $M = 32.8$ years; $t(38) < 1$). In addition, IED ($M = 15.0$, $SD = 1.7$) and HC ($M = 15.9$, $SD = 1.9$) subjects did not differ in years of education, $t(38) = 1.48$, $P = 0.14$. As expected, however, IED subjects evidenced a greater degree of lifetime acts of aggression [Life History of Aggression -Aggression score (Coccaro et al., 1997)] compared to controls (16.9 ± 4.5 vs. 4.5 ± 3.2, $t(38) = 10.00$, $P < 0.001$).

All of the IED subjects also met general criteria for a personality disorder with personality disorder not otherwise specified (NOS) being the most common diagnosis ($N = 15$), followed by obsessive-compulsive personality disorder ($N = 3$), paranoid personality disorder ($N = 2$) and avoidant personality disorder ($N = 2$). Twelve of the 20 IED subjects had a co-morbid Axis I disorder at the time of assessment. Diagnoses consisted of post-traumatic stress disorder ($N = 3$), alcohol abuse ($N = 3$), anxiety disorder NOS ($N = 3$), depressive disorder NOS ($N = 2$), attention deficit hyperactivity disorder ($N = 1$), and adjustment disorder ($N = 1$). This study was approved by the Institutional Review Board and carried out in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from each participant.

2.2. 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-s blocks of 5 face photos for each expression type (Angry, Happy, Neutral). Each face block consisted of 5 consecutive trials (without any interstimulus interval) of one emotion type, presented for 4 s each. An emotion identification task (i.e., explicit emotion processing) was employed, where subjects were asked to identify the emotional valence (positive, negative, neutral) of the face by