Amygdala and Orbitofrontal Reactivity to Social Threat in Individuals with Impulsive Aggression

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Background: Converging evidence from animal and human lesion studies implicates the amygdala and orbitofrontal cortex (OFC) in emotional regulation and aggressive behavior. However, it remains unknown if functional deficits exist in these specific brain regions in clinical populations in which the cardinal symptom is impulsive aggression. We have previously shown that subjects diagnosed with intermittent explosive disorder (IED), a psychiatric disorder characterized by reactive aggressive behavior, perform poorly on facial emotion recognition tasks. In this study we employed a social-emotional probe of amygdala-OFC function in individuals with impulsive aggression.

Methods: Ten unmedicated subjects with IED and 10 healthy, matched comparison subjects (HC) underwent functional magnetic resonance imaging while viewing blocks of emotionally salient faces. We compared amygdala and OFC reactivity to faces between IED and HC subjects, and examined the relationship between the extent of activation in these regions and extent of prior history of aggressive behavior.

Results: Relative to controls, individuals with IED exhibited exaggerated amygdala reactivity and diminished OFC activation to faces expressing anger. Extent of amygdala and OFC activation to angry faces were differentially related to prior aggressive behavior across subjects. Unlike controls, aggressive subjects failed to demonstrate amygdala-OFC coupling during responses to angry faces.

Conclusions: These findings provide evidence of amygdala-OFC dysfunction in response to an ecologically-valid social threat signal (processing angry faces) in individuals with a history of impulsive aggressive behavior, and further substantiate a link between a dysfunctional cortico-limbic network and aggression.

Key Words: Intermittent explosive disorder, aggression, fMRI, amygdala, orbitofrontal cortex, emotion, faces

Intermittent Explosive Disorder (IED) is characterized by recurrent acts of impulsive, affectively-driven aggression that are disproportionate to any actual provocation (Coccaro 2003a). Of note, these aggressive acts are not attributable to another psychiatric or neurologic condition. Individuals with IED also have elevated levels of trait anger and hostility (McCloskey *et al.* 2006), and typically have frequent (e.g. twice a week) acts of verbal and physical aggression (Coccaro *et al.* 1998) Recent epidemiological studies suggest that IED is highly prevalent (5% lifetime prevalence) in the United States population (Coccaro *et al.* 2004; Kessler *et al.* 2006) Furthermore, IED confers functional impairment equal to or greater than most other Axis I and Axis II disorders (Coccaro *et al.* 1998; McCloskey *et al.* 2006). Despite the public health impact of IED, relatively little is known about the neurobiology of the disorder. At the neurochemical level, IED appears to be associated with dysregulation of the serotonergic system (Coccaro 1989) However, these deficits have not been linked to specific brain circuits. There is a paucity of information about the functional neuroanatomy of IED, partly because the illness is relatively under-studied in brain imaging research and few ecologically-valid probes exist to examine the functional integrity of brain circuitry relevant to aggression.

Previous basic research on brain regions associated with aggression may provide clues about the relevant functional neuroanatomy of IED. Prior models of human aggression specifically implicate the amygdala and paralimbic prefrontal regions including the dorsal and ventral/orbital medial prefrontal cortex (dMPFC and vMPFC/OFC, respectively) (Davidson *et al.* 2000), based on inferences largely from stimulation and lesion studies in animals, non-human primates and humans. For example, in animals, stimulation of the amygdala promotes aggressive responding (Adamec 1991), whereas its damage leads changes in social interactions (Amaral *et al.* 2003; Izquierdo *et al.* 2005; Kluver and Bucy 1939) In humans, amygdala atrophy and/or lesions have been associated impulsively aggressive behaviors (van Elst *et al.* 2000). Specific damage to the OFC is associated with impulsive and aggressive behavior (Damasio *et al.* 1994; Izquierdo *et al.* 2005; Pribram and Bragshaw 1953), and individuals with such damage show little control over their emotions as well as limited awareness of the moral implications of their actions and poor decision making (Anderson *et al.* 1999; Damasio 1994; Grafman *et al.* 1996) As the amygdala and OFC are both anatomically and functionally connected (Amaral and Price 1984), their effective interactions are appear to be critical for decoding emotionally salient information and guiding goal-directed behaviors (Saddoris *et al.* 2005), which are of relevance to the control of aggression. Moreover, the OFC is hypothesized to play a key role in modulating limbic reactivity to threat (Davidson *et al.* 2000; Izquierdo *et al.* 2005).

The link between aggression and the amygdala-prefrontal circuit has also been supported by studies of clinically aggressive populations, though not IED per se. There is evidence to suggest that aggressive behavior related to a variety of psychiatric diagnoses (borderline personality disorder (Juengling *et al.* 2003), impulsive personality disorder, antisocial personality disorder [ASPD]) is associated with dysfunction in the vMPFC and amygdala (Blair 2003; Siever *et al.* 1999; Soloff *et al.* 2000; Tebartz van Elst *et al.* 2003). In particular, early PET studies by Raine and colleagues (Raine *et al.* 1994, 1997) showed that murderers, and more specifically affective murderers, have decreased prefrontal and increased subcortical metabolism compared to matched controls (Raine *et al.* 1998). Subsequently, New

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et al. (2002) have shown that impulsive aggressive personality disordered patients exhibit blunted prefrontal, including the vMPFC and OFC, metabolism in response to a serotonergic challenge. Although these studies suggest a potential abnormal limbic-prefrontal function in aggressive individuals, the findings may not generalize to patients with IED or directly reflect functional responses to probes aimed at provoking aggressive responding.

Functional 'activation' neuroimaging studies have begun to use emotion induction and/or processing paradigms to probe amygdala-prefrontal function related to anger and aggression in healthy and psychiatric samples. Anger-inducing script imagery has been associated with prefrontal, including vMPFC and OFC, activation in healthy subjects (Damasio *et al.* 2000; Dougherty *et al.* 1999). Interestingly, Dougherty and colleagues demonstrated vMPFC hypoactivity and differential vMPFC-amygdala interactions in response to anger-inducing script imagery in depressed patients with anger attacks (Dougherty *et al.* 2004). Similar studies of subjects with borderline personality disorder (BPD), often associated with increased anger, aggression and impaired affective regulation, have observed OMPFC hypoactivity and amygdala hyperactivity during processing of emotionally negative stimuli (Donegan *et al.* 2003; Herpertz *et al.* 2001; Schmahl *et al.* 2004). However, these paradigms have not been conducted in subjects with impulsive aggression.

One validated, laboratory-based probe of socio-emotional information processing is the emotional face discrimination task (Ekman 2003). Facial expressions act as potent nonverbal signals between humans, imparting emotional salience to social interactions (Darwin 1872/1965; Ekman 2003) Interestingly, individuals with IED perform poorly relative to healthy controls in recognizing the emotional expression hostile intent to neutral or benign situations including neutral facial expressions (Best *et al.* 2002) and are hyper-responsive to actual provocation/threat (McCloskey *et al.* 2006) Deficits in socio-emotional information processing (e.g., perceiving neutral faces as threatening) among IED patients suggest dysfunctional responses in the amygdala-prefrontal circuit, which is known to mediate the interpretation of emotional cues from faces (Adolphs 2002) In humans, discrete lesions to the amygdala impair recognition of fear/threat and recognition of other socially salient expressions (Adolphs *et al.* 2002, 2005). Processing faces that convey anger has been associated with amygdala and vMPFC/OFC activation (Blair *et al.* 1999; Nomura *et al.* 2004) This link between amygdala-OMPFC dysregulation and socio-emotional information processing is of particular importance to aggression research. At a neurofunctional level, the same amygdala-prefrontal circuit critical to social cognition also serves to regulate emotion and behavior, including anger and aggression (Beer *et al.* 2003; Davidson *et al.* 2000; Ochsner and Gross 2005) Indeed, socio-emotional information processing deficits are seen as a causal antecedent in the evocation of maladaptive emotional and behavioral (including aggressive) responses (Crick and Dodge 1996; Walz and Benson 1996).

Therefore, the current study employed functional magnetic resonance imaging (fMRI) and a well-validated facial emotion processing task, known to reliably probe amygdala-prefrontal function, in order to compare brain responses between IED subjects and matched healthy controls (HC). Based on existing data, we hypothesized: 1) that patients with IED would have greater amygdala and less prefrontal (specifically vMPFC/OFC) activation to faces that conveyed direct social threat (e.g., angry and/or fearful faces) relative to controls; 2) that functional interactions between the amygdala and vMPFC/OFC would be different between IED and HC subjects; and 3) that amygdala activation to threat-related stimuli would be correlated with clinical measures of the extent of prior aggressive behavior.

Methods and Materials

Participants

Ten subjects with IED-IR (Coccaro 2003b) and 10 healthy control (HC) subjects participated in this study. The diagnosis of IED-IR was based on Integrated Research Criteria for IED as first described by Coccaro (Coccaro 2003b); IED-IR integrates DSM-IV criteria for IED (American Psychiatric Association 2000) with Research Criteria for IED (Coccaro *et al.* 1998). Other Axis I and Axis II psychiatric diagnoses were made according to DSM-IV criteria. Final diagnoses were assigned through a best estimate (BE) process (Klein *et al.* 1994; Leckman *et al.* 1982) based on information from a variety of sources including a series of structured clinical interviews administered by trained masters or doctoral level clinicians. Structured clinical interviews included the Structured Clinical Interview for DSM Diagnoses (SCID-I; (First *et al.* 1995)) for the diagnosis of Axis I disorder, the IED-IR Interview Module (IED-M; (Coccaro)) for the diagnosis of IED-IR, and the Structured Interview for the Diagnosis of DSM-IV Personality Disorder (SIDP-IV; (Pfohl *et al.* 1995)) for the diagnosis of Axis II Personality Disorder (PD). These data were supplemented by information obtained by a research psychiatrist, in a separate clinical interview. Clinical data were compiled and final consensus past and current Axis I and II diagnoses were assigned by a BE panel including at least two psychiatrists and two clinical psychologists. This methodology has previously been shown to enhance the accuracy of diagnosis over direct interview alone (Kosten and Rounsaville 1992). Additional behavioral assessments included the global assessment of functioning (GAF) (American Psychiatric Association 2000), Lifetime History of Aggression scale (LHA) (Coccaro *et al.* 1997), the Buss-Perry aggression questionnaire (BPAQ) (Buss and Perry 1992), State-Trait Anger Expression Inventory (STAXI) (Spielberger 1996), and Beck Depression Inventory (BDI) (Beck *et al.* 1961) None of the IED subjects had any history of autism/pervasive developmental disorders, mental retardation, significant medical or neurological illness, or met criteria for current major depressive episode (MDE) at the time of scanning. Five of the IED subjects had a life history of other Axis-I disorders (1 with childhood attention deficit hyperactivity disorder and cannabis abuse in full remission, 1 with specific phobia-animal type, 1 with MDE and alcohol dependence in full remission, 1 with generalized anxiety disorder, and 1 with alcohol abuse in full remission) and all of the IED subjects were determined to have at least one Axis II Personality Disorder (6 with PD not otherwise specified, 1 with borderline PD, 1 with narcissistic PD and obsessive compulsive PD (OCPD), 1 with paranoid PD and narcissistic PD, 1 with OCPD). Of note, none met criteria for antisocial PD. Healthy controls had no current or past history of any Axis I or Axis II disorder and none had a first degree relative with documented history of Axis I disorder. All subjects were right-handed and had normal, or corrected to normal vision. Two IED subjects were previously treated with antidepressant medications (prior to 8 weeks of scan), but none of the subjects (IED and HC) were on psychoactive medications at the time of scanning. Subjects were matched on age and gender, and race/ethnicity and educational background (Table 1). As expected, IED subjects reported significantly greater extent of prior aggression based on the LHA-A

Table 1. Group Demographics (Mean ± SD)

	IED (n = 10)	HC (n = 10)	p Value[e]
Age (years)	34.3 ± 7.3	30.9 ± 5.6	n.s
Gender	5F/5M	5 F/5M	-
Race/Ethnicity	5C/1 O	7 C	-
	3 AA/1 AsA	2 AA/1 AsA	-
Education[a]	15.6 ± 1.3	13.4 ± 1.0	<.001
SES	36.4 ± 13.8	36.4 ± 17.4	ns
GAF	57.8 ± 6.8	83.0 ± 5.3	<.001
Lifetime Aggression[b]	21.5 ± 2.0	5.3 ± 2.6	<.001
BPAQ-tot	86.2 ± 25.7	70.7 ± 18.9	ns
Trait Anger[c]	27.6 ± 8.2	13.6 ± 3.4	<.001
State Anger[c]	27.3 ± 14.9	15.3 ± .7	<.03
Current Depression[d]	11.6 ± 10.9	.3 ± .7	<.01

IED, Intermittent Explosive Disorder; HC, Healthy Control subjects; F, Female; M, Male; AsA, Asian American; AA, African American; C, Caucasian; O, Other; SES, Socio-economic status; GAF, Global Assessment of functioning scale; BPAQ, Buss-Perry aggression questionnaire total score.

[a]Based on years of education.

[b]History of aggression as measured by the Lifetime History of Aggression-Aggression subscale (LHA-A) Scale.

[c]State-Trait Anger Expression Inventory (STAXI).

[d]Beck Depression Inventory (BDI).

[e]Group differences tested with 2-sample t-tests; ns, not significant ($p >$ .1, 2-tailed).

(aggression subscale) and trait levels of anger/aggression/hostility based on STAXI, and BPAQ scores compared to HC subjects. Relative to HC subjects, IED subjects also had lower GAF scores, and higher, though minimal, levels of depression as assessed by BDI (Table 1). All subjects provided written informed consent for this study, as approved by the University of Chicago Institutional Review Board.

Tasks and Materials

The stimuli comprised of black and white photographs of human facial expressions from the standardized Ekman and Friesen set (Ekman and Friesen 1976) Via MRI-compatible goggles inside the scanner, subjects viewed the photos in a series of 20 sec blocks of 10 face photos for each expression type (angry, disgusted, fearful, happy, neutral, sad, surprised); each face block consisted of 10 consecutive trials (without any interstimulus interval) of one emotion type, presented for 2 sec each. An on-line gender identification (e.g., implicit emotion processing) task was employed, where subjects were asked to identify the gender (male, female) of the face by button-press. Face blocks were interspersed with 20 sec 'Rest' blocks (in order to allow the fMRI activation to the face blocks to return to baseline) of blank, gray-screens during which subjects were told to make a button-press with each new image. Each emotion expression type was presented per run (6 total runs), and the block order was pseudorandom across runs and subjects. Outside the scanner, all subjects performed an emotion expression recognition task (explicit emotion processing) following the fMRI experiment.

Functional MRI Data Acquisition

Imaging was performed with blood oxygen level dependent (BOLD)-sensitive whole-brain fMRI on a 3 Tesla GE Signa System (Milwaukee, Wisconsin) using a standard radiofrequency coil and updated software (LX 8.3, Neuro-optimized gradients). To minimize susceptibility artifact, whole-brain functional scans were acquired using a T2*-weighted reverse spiral gradient-recall-echo (GRE) sequence (time-to-echo (TE) = 25 msec, repetition time (TR) = 2000 msec, 64x64 matrix, flip angle of 77°, field of view (FOV) of 24 cm, 30 contiguous 5mm sagittal slices per volume, aligned with the AC-PC line) (Noll *et al.* 1999) A high-resolution T1 scan was acquired to provide precise anatomical localization (3D-MPRAGE, TR of 25 msec, min TE, FOV of 24 cm, slice thickness of 1.5 cm), to rule out structural abnormalities and anatomic localization. Head movement was minimized by using foam inserts placed around the head and neck within the head coil.

Functional MRI Data Analysis

Data from all 20 subjects 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 SPM2 (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 an EPI template in Montreal Neurologic Institute (MNI) space, resampled to 2 mm^3 voxels, and smoothed with an 8 mm^3 kernel to minimize noise and residual differences in gyral anatomy. The general linear model was applied to the time series, convolved with the canonical hemodynamic response function (Friston *et al.* 1995) and with a 128 sec high-pass filter. Condition effects were modeled with box-car regressors representing the occurrence of each block type. Condition effects were estimated at each voxel, and for each subject, statistical parametric maps (SPMs) were produced from linear contrasts of interest: (1) each face category versus baseline (e.g., angry face > rest). We opted to use the 'rest' periods as the control condition for several reasons: 1) to maximize power to detect amygdala activation and potential differences in activation between groups given that 'neutral', expressionless faces have been shown to also activate the amygdala to the same extent as emotional faces (Fitzgerald *et al.* 2006; Somerville *et al.* 2004; Wright and Liu 2005); 2) differential amygdala activation to neutral faces between IED and HC subjects may render the 'control' condition incomparable in between-group comparisons (Gusnard and Raichle 2001); and 3) IED subjects have been shown to mislabel 'neutral' faces as conveying negative emotions (Best *et al.* 2002).

Differential brain activation between groups (IED vs. HC) was initially examined with voxel-wise analyses within a 2nd-level random effects model using a 2 (Group) × 7 (Expression) analyses of variance (ANOVA) in order to detect significant main or interaction effects. This was followed by 2-sample t-tests (IED > HC; HC > IED) from single-subject linear contrasts of interest (e.g., anger > rest); these t-statistics were transformed to Z-scores in SPM2. Outside of a priori regions of interest (amygdala, orbitofrontal cortex), we report all regions containing activation foci with Z-scores > 2.68 (corresponding to a $p < .005$, uncorrected for multiple comparisons) with an extent threshold of > 20 contiguous voxels/cluster, in order to compare to prior relevant functional brain imaging studies, to generate new hypotheses for subsequent imaging studies of aggression, and to obviate bias. However, we also had specific a priori hypotheses about two discrete regions of interest (ROI), amygdala and ventral medial prefrontal/orbitofrontal cortex. These ROIs were defined using anatomically-derived, atlas-based masks (Walter *et al.* 2003), using boundaries from the atlas of Tzourio-Mazoyer and colleagues (Tzourio-Mazoyer *et al.* 2002). The amygdala search volume comprised 220 2mm^3 voxels (approximately 1.8 cm^3) on each side (left, right) and the OFC search volume comprised 4024 2 mm^3 voxels (approximately 32.2 cm^3). Significant between-

group differences activation in a priori regions (amygdala, OFC) were additionally confirmed via two complementary approaches: 1) an ROI-based voxel-wise test of significance based on activation strength ($p < .05$, corrected for multiple comparisons across the anatomical-based amygdala and OFC ROIs (Walter *et al.* 2003) using the small volume correction (SVC) toolbox within SPM2 (Worsley *et al.* 1996) in which suprathreshold voxels were corrected for the false discovery rate (FDR) (Genovese *et al.* 2002) in order to reduce Type I error) and on activation extent (clusters > 20 contiguous voxels) of activation; 2) 2-sample *t*-tests of extracted parameter estimates of activation (β weights, arbitrary units [a.u.]), an index of BOLD signal change, from amygdala and OFC ROIs using MarsBaR software (http://marsbar.sourceforge.net) (significance was set at $p < 05$, 2-tailed). We also calculated Cohen *d*, an index of effect size, based on the following: Cohen's d = mean PSC_{IED} – mean PSC_{HC}/σ_{pooled}, where $\sigma_{pooled} = \sqrt{(\sigma_{IED}^2 + \sigma_{HC}^2)/2}$; (σ = Standard Deviation [SD]).

Results

Behavioral Results

For the on-line task, there were no group differences ($p > .2$) in gender-identification accuracy, with both groups achieving > 99% correct responses. Analysis of post-scan emotion recognition accuracy revealed that subjects had high accuracy rates across emotions (avg. percent correct = 83 ± 7%). There was a significant main effect of emotion on recognition accuracy ($F = 6.76$, $p < .0001$); however, there were no significant group differences in accuracy of recognition on any specific emotion (all $p_s > .2$) (Table 2).

Functional MRI Results

Results of the 2 (Group) x 7 (Expression) ANOVA showing activation foci with a significant main effect of Group, main effect of Expression, and Group x Expression interactions are shown in Table 3. As predicted, the there was a significant Group x Expression interaction at the left amygdala (MNI coordinates of maximal foci: [-18,2,-22]; $F_{[6,126]} = 3.13$, $p = .007$; Z = 2.47) and in the OFC ([-16, 38, -4]; $F_{[6,126]} = 3.20$; $p = .006$; Z = 2.52). Follow-up 2-sample *t*-tests showed that IED subjects exhibited greater left amygdala activation in response to angry faces compared to HC subjects (Table 4; Figure 1A). Of note, there were no significant group differences in amygdala activation to other emotional expressions (Table 4; Figure 1C). The IED > HC amygdala activation to angry faces was also confirmed by results from the ROI-based analysis of extracted BOLD response (Mean β weights [a.u.] ± SEM, IED: .30 ± .07 vs. HC: .04 ± .06; Cohen $d = 1.18$; $t_{18} = 2.57$, $p = .019$, 2-tailed) (Figure 1C). As suspected, we observed that, compared to the HCs, the IED group exhibited greater amygdala activation to "neutral" faces (albeit at trend-level significance, $p = .09$, 1-tailed), supporting our approach to use "Rest" blocks as the control condition. Direct comparisons of the extracted BOLD response in the amygdala ROI between each emotional expression (including angry) and neutral expression did not reveal significant group differences (all $p_s > .2$). In response to angry faces (but not other emotionally negative expressions), OFC activations were greater in the HC subjects relative to IED subjects (Table 5). OFC responses to happy faces were also observed to be greater in HC than IED subjects. As shown in Table 5, there were no areas of hypoactivity in IED subjects (HC > IED) shared across all facial expressions. However, activation of the rostral and dorsal medial frontal gyrus was greater in HC than IED subjects across five expressions (fearful, happy, neutral, surprised, sad); a similar pattern (HC > IED) was observed in the middle frontal gyrus in five expressions (angry, happy, neutral, surprised, sad), superior frontal gyrus in four expressions (angry, disgusted, fearful, sad), and middle temporal gyrus in four expressions (disgusted, fearful, neutral, sad) (Table 5).

Given the extensive anatomical (Amaral and Price 1984; Price 2003) and functional connections (Kringelbach and Rolls 2004; Saddoris *et al.* 2005) between amygdala and OFC (specifically Brodmann Area [BA] 11m), we performed interregional correlation analyses in order to examine the relationship between BOLD signal change within in the left amygdala and those across the prefrontal cortex. A functional connectivity analysis was carried out using the Physiologic-Physiologic Interaction SPM Toolbox (Friston *et al.* 1997) by extracting raw BOLD signal using the entire time series from the left amygdala ROI (e.g., seed region) and entering these values into a whole-brain regression analysis. The resulting positive and negative correlation contrast images for each subject were then entered into 2nd level random effects analyses for each group separately to identify significant correlations ($p < .05$, corrected for multiple comparisons across the OFC ROI). As expected, we observed differential interactions (e.g., coupling) of amygdala-OFC within the IED and HC groups. In the HC group, a negative correlation between BOLD signal changes in the left amygdala and those of OFC was detected (Montreal Neurological Institute [MNI] coordinates of maximal correlation: medial OFC: [6, 52, -20], Z = 3.87, k = 167 voxels, $r = -.79$, $p < 005$; lateral OFC: [46, 50, 0], Z = 2.30, k = 68 voxels; $r = -.61$, $p < 01$). A direct comparison in strength of correlation between IED and HC groups revealed that the HC had greater amygdala-related connectivity in the medial OFC (BA 10/ 11m) ([6, 52, -20], Z = 2.84, $p = .005$ uncorrected) than the IED group. Of note the medial OFC foci and its associated cluster is localized to BA 10 extending into BA 11m (Figure 2), which has been shown to have direct projections to amygdala (Cavada *et al.* 2000; Ghashghaei and Barbas 2002; Ongur *et al.* 2003); however, the lateral OFC foci is located in BA 10, which has not been shown in animal studies to have direct connections with amygdala. No positive correlations between amygdala-OFC signal were detected in HC subjects. In contrast, no correlations (positive or negative) between amygdala and OFC signal were observed in IED subjects, even when the statistical threshold was lowered to $p < .05$, uncorrected.

In order to examine a brain-behavior relationship between amygdala activation to angry faces and extent of lifetime history of aggressive behavior, we obtained a Pearson's correlation coefficient between extracted BOLD response (β weights) and Lifetime History of Aggression-Aggression Subscale (LHA-A)

Table 2. Emotion Recognition Accuracy (%Correct: Mean ± SD)

	IED ($n = 10$)	HC ($n = 10$)	*p* Value[a]
Anger	81 ± 7	76 ± 26	ns
Disgust	74 ± 18	67 ± 30	ns
Fear	79 ± 15	74 ± 16	ns
Happy	98 ± 4	99 ± 2	ns
Sad	82 ± 13	80 ± 17	ns
Surprise	89 ± 15	94 ± 6	ns
Neutral	89 ± 13	79 ± 23	ns

IED, intermittent explosive disorder; HC, healthy control subjects.
[a]Group differences tested with 2-sample *t*-tests; ns, non-significant ($p >$ .1, 2-tailed).

Table 3. Brain Regions Showing Significant Activation in the 2 (Group) X 7 (Expression) ANOVA: Whole-Brain Voxel-Wise Analysis

Main Effect/Interaction	Region	Side	MNI Coordinates			Cluster Size	Z Score[a]
			x	y	z		
Group	Middle Temporal Gyrus	R	52	-80	14	3009	6.56
	Lingual Gyrus	L	-12	-96	-14	1828	6.05
	Middle Frontal Gyrus	L	-26	50	26	6183	5.42
	Middle Occipital Gyrus	L	-46	-84	-4	898	5.06
	Precentral Gyrus	L	-36	-6	40	295	4.80
	Paracentral Lobule	L	-4	-42	52	623	4.38
	Superior Frontal Gyrus	L	-8	0	76	37	3.98
	Medial Frontal Gyrus	L	-8	4	-22	97	3.93
	Cerebellar Tonsil	R	36	-60	-44	240	3.92
	Superior Temporal Gyrus	L	-68	-44	14	312	3.91
	Culmen	L	-40	-48	-28	92	3.82
	Superior Occipital Gyrus	R	30	-82	26	81	3.72
	Middle Frontal Gyrus	R	40	20	50	146	3.70
	Fusiform Gyrus	L	-40	-74	-20	150	3.68
	Brainstem	L	-8	-16	-34	28	3.65
	Cuneus	L	-10	-98	24	35	3.57
	Caudate	R	24	-32	24	95	3.52
	Superior Frontal Gyrus	R	32	52	-16	132	3.51
	Postcentral Gyrus	L	-26	-48	62	118	3.50
	Postcentral Gyrus	R	26	-40	50	152	3.50
	Anterior Cingulate	L	-10	10	24	38	3.47
	Middle Temporal Gyrus	L	-54	-18	-18	58	3.44
	Parahippocampal Gyrus	R	24	-10	-30	84	3.41
	Posterior Cingulate	R	28	-62	10	36	3.36
	Supramarginal Gyrus	L	-38	-56	34	72	3.24
	Culmen	R	10	-62	-6	113	3.22
	Inferior Parietal Lobule	L	-44	-58	54	148	3.19
	Inferior Frontal Gyrus	R	52	26	2	204	3.15
	Declive	R	42	-82	-28	28	3.10
	Precentral Gyrus	R	46	-18	48	28	2.86
	Precuneus	R	16	-56	34	24	2.77
Emotion	Inferior Frontal Gyrus	L	-18	12	-22	48	3.50
Group x Expression	**Amygdala**	**L**	**-18**	**2**	**-22**	**31**	**2.47**
	OFC	**L**	**-16**	**38**	**-4**	**33**	**2.52**

MNI, Montreal Neurological Institute; L, Left; R, Right; ANOVA, analysis of variance; OFC, orbitofrontal cortex.

[a]Z-scores and significance based whole-brain voxel-wise $p < .005$ uncorrected, clusters > 20 contiguous voxels. Areas in bold represent a priori regions of interest whose suprathreshold voxels exceeded a threshold of $p < .05$ uncorrected.

scores. As predicted, a significant positive correlation was observed ($r = .546$, $p < .02$) (Figure 1B).

Discussion

To our knowledge, this is the first fMRI study to examine brain activation, specifically amygdala-OFC function, during emotional information processing among IED patients with an extensive history of impulsive, reactive aggression. The study probed the neuroanatomy of impulsive aggression in a clinical population to elaborate on prior findings from human lesion and animal studies. We demonstrate a putative link between amygdala-OFC dysfunction and impulsive aggression in IED on three levels of evidence: 1) exaggerated amygdala and diminished OFC reactivity to faces conveying direct threat (anger) in IED subjects relative to controls; 2) lack of amygdala-OFC functional connectivity during the face processing task in IED subjects, but a significant reciprocal (inverse) interaction between amygdala and OFC in controls; and 3) direct, positive correlation between amygdala reactivity to angry faces and extent of prior aggressive behavior.

The results show that even in the absence of group differences in emotion perception performance (e.g., expression recognition accuracy), differences in discrete brain regions in response to certain emotions were detectable between IED and HC subjects. We observed exaggerated reactivity in the amygdala of IED subjects in response to angry faces, but not to any other facial expression, indicating that the response in the IED group is aberrant in response to interpersonal cues that convey direct threat against the observer (Adams *et al.* 2003) This finding of threat-related amygdala hyperactivity in IED suggests that limbic hyper-arousal in this clinical disorder may not be generalized across other types of emotional stimuli. In contrast, patients with BPD, who are partly characterized by aggressive behaviors and pervasively poor affective regulation, have been shown to exhibit amygdala hyperactivity across a number of emotionally positive, negative, and neutral facial expressions (Donegan *et al.* 2003); thus, the underlying neuropathophysiology between IED and BPD may be different, despite both disorders sharing symptoms consistent with dysfunctional control of emotional states.

The finding of amygdala hyperactivity to angry faces also differentiates IED, which is defined by impulsive, reactive aggression, from antisocial PD and psychopathy, which are associated with the disregard for and violation of the rights of others

Table 4. Brain Regions Showing Greater Activation in IED (> HC) Subjects in Response to Each Facial Expression Condition (Relative to Rest): Whole-Brain Voxel-Wise Analysis

Expression	Region	Side	MNI Coordinates			Cluster Size	Z Score[a]
			x	y	z		
Angry	**Amygdala**	**L**	**-22**	**0**	**-26**	**78**	**3.06**
	Brain Stem	L	-2	-30	-8	117	3.63
	Superior Temporal Gyrus	R	60	-34	12	24	3.08
Disgusted	Brain Stem	R	6	-34	-22	51	3.80
	Fusiform Gyrus	R	40	-46	-26	49	3.61
Fearful	Middle Occipital Gyrus	L	-20	-102	2	135	3.19
	Thalamus	L	-6	-16	-2	22	2.97
Happy	Cingulate Gyrus	L	-22	-28	44	106	3.59
	Lingual Gyrus	R	28	-72	-6	79	3.17
Neutral	Lingual Gyrus	L	-12	-90	-12	131	3.57
	Precuneus	R	26	-44	38	30	3.55
	Cerebellum	R	0	-40	-40	68	3.53
	Inferior Occipital Gyrus	L	-40	-86	-14	77	3.47
	Cerebellum	R	6	-36	-14	29	3.33
	Fusiform Gyrus	R	48	-60	-14	79	3.29
	Caudate	L	-16	-12	24	53	3.22
	Parahippocampal Gyrus	L	-26	4	-10	58	3.18
	Lentiform Nucleus	R	10	0	-10	25	3.07
	Brainstem	R	6	-12	-20	28	2.98
	Fusiform Gyrus	L	-44	-54	-16	27	2.88
	Cerebellum	L	-12	-36	-24	40	2.87
	Lingual Gyrus	L	-10	-70	-2	31	2.85
	Caudate	L	-4	14	6	30	2.81
Surprised	Caudate	L	-24	-28	26	52	3.63
	Middle Temporal Gyrus	L	-32	-62	12	33	3.58
	Putamen	L	-24	14	14	81	3.35
Sad	Medial Occipital Gyrus	L	-18	-106	-8	31	3.11

IED, Intermittent Explosive Disorder; HC, Healthy Control subjects; MNI, Montreal Neurological Institute; L, Left; R, Right.

[a]Z-scores and significance based whole-brain voxel-wise $p < .005$ uncorrected, clusters > 20 contiguous voxels. Areas in bold represent a priori regions of interest whose suprathreshold voxels additionally exceeded a $p < .05$ corrected for multiple comparisons based on the false discovery rate across a small volume.

and with instrumental, goal-directed aggression; it should be noted that although psychopaths are more likely to exhibit proactive, purposeful aggression, they also engage in reactive, impulsive, affective aggression (Blair *et al.* 2006) Interestingly, prior studies of individuals with conduct disorder, antisocial PD and/or psychopathy have implicated amygdala dysfunction, although they have been equivocal about whether the amygdala is hyper or hypo-active in these subjects (Blair *et al.* 2006) Some have demonstrated blunted emotional and amygdala responses to fear conditioning (Birbaumer *et al.* 2005), to negative pictures (Sterzer *et al.* 2005), and during affective memory tasks (Kiehl *et al.* 2001), while other studies have observed that patients with antisocial PD/psychopathy exhibit increased amygdala responses to negative pictures (Muller *et al.* 2003) and during aversive emotional conditioning (Schneider *et al.* 2000).

Although previous studies have linked amygdala activation to fearful/afraid faces (Phan *et al.* 2002), some data suggest that the amygdala is also sensitive to angry faces in healthy adults (Fitzgerald *et al.* 2006; Nomura *et al.* 2004; Strauss *et al.* 2005). The observation that IED subjects evoke a heightened amygdala response to angry faces provides evidence for a potentially specific brain-behavior mechanism in the neuropathophysiology of impulsive aggression. We also observed that the extent of amygdala activation to angry faces in individual subjects was related to how aggressive they had been in their lifetime, as indexed by LHA-A scores. This finding shows a linear relationship between aggression as a continuous dimensional variable and amygdala activation to social threat. This is important for two reasons. First, aggression is a dimensional construct, with IED representing the severe end of a continuum (McCloskey et al, unpublished data). Thus a significant finding using a continuous measure of aggression better approximates aggression, as it truly exists. Second, the results suggest that dysfunction in the amygdala may underlie impulsive aggressive responding under social provocation in all subjects, not only clinically aggressive populations.

We also observed that the response to angry faces in the OFC was attenuated in IED subjects, relative to controls, suggesting hypofunction of this important neuromodulatory region during social threat responding (Izquierdo and Murray 2004; Izquierdo *et al.* 2004). Unlike differential amygdala responses to emotional evocation across aggressive disorders, deficits in the orbitofrontal lobes as represented by atrophy, lesion, or hypoactive metabolism have been observed across a number of psychiatric populations prone to aggression (e.g., ASPD, psychopathy, BPD, IED) (Birbaumer *et al.* 2005; New *et al.* 2002; Raine *et al.* 1998, 2000; Siever *et al.* 1999; Soloff *et al.* 2003; Woermann *et al.* 2000) The finding in the current study that the OFC is hypo-responsive to angry faces in IED subjects supports the aforementioned literature, and suggests that OFC hypofunction may be a common

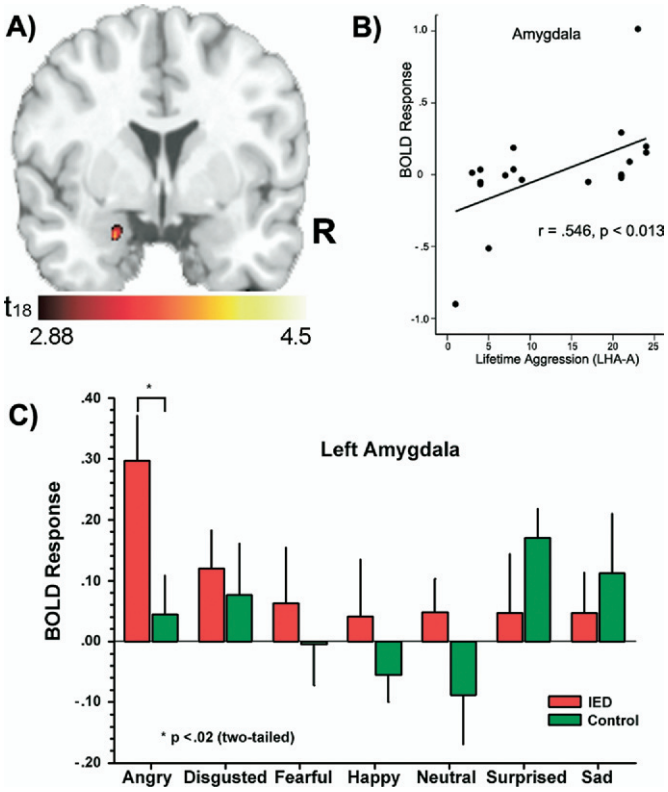

Figure 1. (A) Statistical parametric *t*-map showing greater left amygdala activation to angry faces in IED than in healthy controls based on voxel-wise whole-brain analysis (thresholded at $p < .005$ uncorrected); **(B)** Pearson's correlation between left amygdala activation to angry faces and extent of prior aggressive behavior; **(C)** Box plot of extracted parameter estimates of activation for each face expression (β weights of BOLD Response, arbitrary units [a.u.]) from the anatomically-based left amygdala ROI showing significantly greater amygdala reactivity in IED (vs. NC) subjects only to angry faces (* $p < .02$, 2-tailed, $t_{18} = 2.57$). SPM *t*-map overlaid on coronal slice of a canonical brain rendering constructed using MRIcro software (C. Rorden, M. Brett: http://www.sph.sc.edu/comd/rorden/mricro.html). L, left; R, right; IED, intermittent explosive disorder subjects; HC, healthy control subjects; ROI, regions of interest; BOLD, blood oxygen level dependent.

mechanism underlying the pathophysiology of aggressive behavior in general (e.g., both impulsive and premeditated forms).

We also observe that responses in several regions of the prefrontal cortex (medial, middle, superior frontal gyrus) during the perception of salient faces (across a number of expressions) were greater in controls than IED subjects. Collectively, these regions, including the vMPFC/OFC have been implicated in the cognitive appraisal of emotionally salient stimuli and control of evoked affective states (Ochsner and Gross 2005) This finding is consistent with prior studies showing individuals with a history of anger and aggression problems having blunted vMPFC/OFC responses to anger induction and serotonergic challenges (Dougherty *et al.* 2004; New *et al.* 2002) The vMPFC/OFC has been specifically implicated in a variety of areas pertinent to IED including the regulation of negative affect and aberrant behaviors such as aggression (Blair *et al.* 1999; Damasio *et al.* 1994; Davidson *et al.* 2000; Pribram and Bragshaw 1953; Urry *et al.* 2006), appraisal of emotionally salient stimuli (Ochsner and Gross 2005), and social-moral judgment (Anderson *et al.* 1999; Damasio *et al.* 1994). Furthermore, transcranial magnetic stimulation of the MPFC specifically impairs the recognition of angry facial expressions (Harmer *et al.* 2001).

Our functional connectivity analysis revealed that the OFC did not engage in regulatory interaction with the left amygdala (which was hyperactive) of IED subjects, whereas healthy control subjects demonstrated strong and reciprocal coupling between these regions. The amygdala and OFC share direct and indirect bidirectional connections and are tightly functionally linked (Amaral and Price 1984; Price 2003) Dynamic, modulatory amygdala-OFC interactions is critical to effective emotion regulation and control of aggression (Davidson *et al.* 2000; Izquierdo *et al.* 2005; Urry *et al.* 2006), which is partly based on successful decoding of the value of incoming stimuli and facilitation of goal-directed behavior that is optimal for survival (Saddoris *et al.* 2005) In healthy subjects this is evidenced by reciprocal relationship during the experience of negative affective states, including anger, in which the OFC serves as the mediator of the amygdala's response (Dougherty *et al.* 2004; Urry *et al.* 2006). However, among depressed subjects with a history of anger attacks, the reciprocal/inverse interaction between amygdala and vMPFC was not detected (Dougherty *et al.* 2004) Collectively, these findings suggest that in impulsively aggressive subjects, the OFC/vMPFC is not recruited during processing of salient faces to exert control of amygdala reactivity, and that an uncoupling of amygdala-OFC circuitry may be relevant to the neuropathophysiology of aggressive disorders.

The study has several limitations worth discussion. First, the small sample size limits definitive conclusions until the findings are replicated in larger samples. Second, for reasons noted above, we opted to use the "rest" blocks as the control condition in our analysis of group differences. Therefore, the results should be interpreted cautiously and in the context that findings from contrasts against the "rest" baselines/control conditions are less specific than those against "neutral" faces, which affords an additional control for general, "non-emotional" face processing. Moreover, although the data shown in Figure 1C is suggestive of a group difference (IED > HC) in response to angry (> neutral) faces, direct comparisons of the extracted BOLD response from the amygdala ROI revealed that these differences were nonsignificant due to intersubject variability; therefore, the current data does not fully support an inference of specificity of the effect. Third, given that this was the first fMRI study of IED, we opted to report activations surpassing a relatively low statistical threshold ($p < .005$ uncorrected for multiple comparisons) which may have introduced Type I errors; however, based on our results, future studies would be justified in focusing a priori on the amygdala and related paralimbic prefrontal regions. Fourth, we did not examine brain responses in other aggressive populations (BPD with aggressive behaviors, MDD with anger attacks, ASPD/psychopathy, etc.) and therefore, our findings may not be comparable and/or generalizable. Fifth, we limited our IED sample to subjects without currently active depression, though allowed for past Axis I and II co-morbidity, in order to study a representative IED population, which may have partly affected the results. Future studies employing other comparison groups and/or matching across co-morbid disorders are needed to clarify these important issues. Sixth, although we used a valid, well-studied socio-emotional processing task (e.g., emotional face discrimination) in order to probe amygdala function, the study did not examine brain responses under direct evocation of anger or aggressive behavior. Future studies that employ such probes (e.g., Point Subtraction Aggression Paradigm, Taylor Aggression Paradigm) are much needed to examine amygdala-OFC reactivity during active aggressive provocation. Furthermore, the relatively small sample size may have obscured group

Table 5. Brain Regions Showing Greater Activation in HC (> IED) Subjects in Response to Each Facial Expression Condition (Relative to Rest): Whole-Brain Voxel-Wise Analysis

Emotion	Region	Side	MNI Coordinates			Cluster Size	Z Score[a]
			x	y	z		
Angry	**Orbitofrontal Cortex**	R	**32**	**46**	**-16**	**300**	**2.80**
	Superior Frontal Gyrus	R	20	50	18	391	3.55
	Superior Frontal Gyrus	L	-34	64	0	73	3.47
	Superior Frontal Gyrus	L	-22	52	16	105	3.46
	Inferior Parietal Lobule	L	-56	-52	50	44	2.97
	Middle Frontal Gyrus	L	-42	26	44	38	2.96
	Cerebellum	L	-32	-78	-46	31	2.95
	Anterior Cingulate Gyrus	R	16	44	-4	21	2.78
Disgusted	Anterior Cingulate Gyrus	L	-20	20	30	35	3.82
	Precentral Gyrus	R	34	-6	42	137	3.75
	Middle Temporal Gyrus	L	-48	-78	12	62	3.52
	Parahippocampal Gyrus	R	10	2	-20	117	3.27
	Superior Frontal Gyrus	L	-16	38	40	37	3.26
	Precuneus	R	14	-72	26	39	3.14
	Middle Temporal Gyrus	L	-46	-30	-4	20	2.87
Fearful	Medial Frontal Gyrus	R	20	26	36	269	3.73
	Middle Temporal Gyrus	L	-48	-84	16	38	3.58
	Superior Frontal Gyrus	L	-26	46	28	78	3.28
	Brainstem	L	-4	-24	-50	22	3.25
	Medial Frontal Gyrus	R	18	-14	50	23	3.03
	Medial Frontal Gyrus	R	4	56	40	27	2.96
	Precuneus	L	-10	-68	66	24	2.93
	Middle Temporal Gyrus	L	-44	-70	22	28	2.80
Happy	**Orbitofrontal Cortex**	L	**32**	**38**	**-16**	**166**	**3.42**
	Medial Frontal Gyrus	L	-16	52	12	181	4.08
	Inferior Frontal Gyrus	L	-50	28	0	327	3.91
	Parietal Lobule	L	-48	-62	54	146	3.67
	Inferior Temporal Gyrus	L	-50	-6	-38	83	3.65
	Medial Frontal Gyrus	R	16	28	38	51	3.59
	Middle Frontal Gyrus	L	-48	54	8	25	3.55
	Cerebellum	L	-38	-58	-42	92	3.47
	Supramarginal Gyrus	L	-58	-48	24	60	3.39
	Paracentral Lobule	R	4	-42	54	63	3.38
	Parahippocampal Gyrus	L	-30	-10	-30	41	3.38
	Inferior Frontal Gyrus	R	20	12	-24	24	3.28
	Superior Frontal Gyrus	R	6	56	46	37	3.18
	Middle Frontal Gyrus	L	-46	56	-8	77	3.12
	Inferior Frontal Gyrus	L	-52	16	12	23	2.72
Neutral	Supramarginal Gyrus	L	-60	-50	38	241	3.90
	Angular Gyrus	R	42	-70	36	160	3.67
	Medial Frontal Gyrus	L	-10	60	12	149	3.34
	Middle Temporal Gyrus	L	-64	-48	2	22	3.01
	Middle Frontal Gyrus	L	-26	20	30	39	3.00
	Inferior Temporal Gyrus	R	50	-4	-32	32	2.92
Surprised	Medial Frontal Gyrus	R	18	48	16	294	4.06
	Middle Occipital Gyrus	L	-54	-78	16	147	3.52
	Superior Temporal Gyrus	R	60	-60	14	72	3.46
	Uncus	L	-22	8	-22	34	3.39
	Medial Frontal Gyrus	L	-12	44	-18	51	3.3
	Middle Frontal Gyrus	R	34	36	-8	29	3.2
	Inferior Parietal Lobule	L	-64	-52	42	133	3.18
	Inferior Occipital Gyrus	R	48	-80	-6	23	2.98
	Thalamus	L	-6	-8	-4	36	2.97
	Medial Frontal Gyrus	L	-6	40	30	29	2.82
	Superior Temporal Gyrus	L	-52	20	-24	36	2.81
Sad	Parahippocampal Gyrus/Uncus	R	8	2	-24	55	3.82
	Medial Frontal Gyrus	L	-16	46	20	55	3.58
	Parahippocampal Gyrus	R	30	-22	-28	68	3.33
	Middle Temporal Gyrus	L	-50	-82	16	29	3.32
	Superior Frontal Gyrus	L	-20	24	60	63	3.23

Table 5. (continued)

Emotion	Region	Side	MNI Coordinates x	y	z	Cluster Size	Z score[a]
	Medial Frontal Gyrus	R	2	34	-20	62	3.22
	Cerebellum	R	6	-28	-48	47	3.13
	Middle Temporal Gyrus	L	-48	-70	26	65	3.11
	Superior Temporal Gyrus	L	-30	10	-42	24	3.07
	Medial Frontal Gyrus	R	16	50	-6	137	3.06
	Middle Frontal Gyrus	L	-40	58	6	32	2.82

IED, Intermittent Explosive Disorder; HC, Healthy Control subjects; MNI, Montreal Neurological Institute; L, Left; R, Right.

[a]Z-scores and significance based whole-brain voxel-wise $p < .005$ uncorrected, clusters > 20 contiguous voxels. Areas in bold represent a priori regions of interest whose suprathreshold voxels additionally exceeded a $p < .05$ corrected for multiple comparisons based on the false discovery rate across a small volume.

differences in behavioral performance (e.g., recognition accuracy) as well as functional activation in other brain regions and/or conditions (e.g., other expressions). The fact that altered amygdala-OFC functioning was detected in IED subjects despite the small sample size may speak to the salience of this effect. Lastly, it should be noted that this is a cross-sectional study, and the observations made here do not imply causality.

However, there are several strengths of the current study, which represents the first fMRI investigation of IED subjects. The analysis employed both whole-brain and ROI-based analyses using voxel-wise random effects search for activations across the entire brain, and anatomically-defined ROI-specific extraction of BOLD responses to confirm the activation maps and to correlate with clinical measures. The IED subjects were all unmedicated at the time of scan (8 of the 10 subjects were naive to psychotropic medications), and compared to well-matched group of healthy controls. The results of the study could potentially have important implications with respect to interventions for IED. There are currently no empirically supported treatments for IED. Prior studies have shown that selective serotonin reuptake inhibitors (SSRI) may ameliorate the symptoms of IED (Coccaro and Kavoussi 1997), and recent work have suggested that effective treatment with SSRIs in depression is associated with normalization of amygdala hyperactivity (Fu *et al.* 2004; Sheline *et al.* 2001), and in IED is associated with increases in orbitofrontal metabolism (which is diminished pre-treatment) (New *et al.* 2004) Therefore, delineating an aberrant brain circuit in IED may serve to elucidate brain targets for therapeutic intervention. Together, these findings provide compelling mechanistic evidence to support future studies to directly examine the integrity of amygdala-OFC structural connectivity (e.g., diffusion tensor imaging (Kumpfel *et al.* 2000)) and function, by coupling DTI with fMRI of tasks that engage self-regulation of negative affect and aggressive action tendencies. The potential convergence of preclinical, human lesion and patient-oriented functional imaging data on aberrant amygdala-OFC function in aggressive behavior serves as an impetus for future translational research on the complex nature of human violence. (Coccaro, 2003).

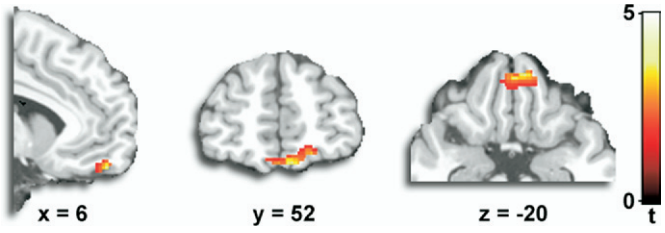

Figure 2. Statistical parametric *t*-map ($p < .05$) showing greater functional connectivity between amygdala and the medial OFC (BA 10/11m) in the HC group compared to IED group. SPM *t*-map overlaid on sagittal (x = 6), coronal (y = 52), and axial (z = -20) slices of a canonical brain rendering constructed using MRIcro software (C. Rorden, M. Brett: http://www.sph-.sc.edu/comd/rorden/mricro.html). L, left; R, right; IED, intermittent explosive disorder subjects; HC, healthy control subjects; SPM, statistical parametric mapping.

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