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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

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.

2.3. Functional MRI data acquisition

Imaging was performed with Blood Oxygen Level Dependent (BOLD)-sensitive whole-brain fMRI on a 3 T GE Signa System (Milwaukee, WI) 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-recalled echo (GRE) sequence (TE = 25 ms, TR = 2000 ms, 64 × 64 matrix, flip angle of 77°, field of view/FOV of 24 cm, 30 contiguous 5 mm axial slices per volume, aligned with the AC-PC line). A high-resolution T1 scan was acquired to provide precise anatomical localization (3D-MPRAGE, TR of 25 ms, min TE, FOV of 24 cm, slice thickness of 1.5 cm) and to rule out structural abnormalities. Head movement was minimized by using foam inserts placed around the head and neck within the head coil.

2.4. Functional MRI data analysis

Data from all 40 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 SPM (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 voxels, and smoothed with an 8 mm 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 and with a 128 s 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 Angry (or Happy) face vs. Neutral face. We wished to use the neutral face as the comparison condition as this putatively was the strictest control for aspects of facial identification and recognition unrelated to emotional information processing. However, the final decision to use neutral face as the control condition was only made after noting that the two groups did not differ in their accuracy in correctly identifying neutral pictures (see Table 1).

Differential brain activation between groups (IED vs. HC) was initially examined with voxel-wise analyses within a 2-level random effects model using 2-sample *t*-tests (IED > HC; HC > IED) from single-subject linear contrasts of interest (e.g., Anger > Neutral); these *t*-statistics were transformed to Z-scores in SPM.

Outside of *a priori* regions of interest, we report all regions containing activation foci with Z-scores >2.99 (corresponding to a $P < 0.001$, uncorrected for multiple comparisons) with an extent threshold of >10 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.

For brain areas where we had a strong specific *a priori* hypothesis, namely the amygdala and ventral medial prefrontal/orbitofrontal cortex, region of interest (ROI) analyses were performed using anatomically-derived, atlas-based masks (Walter et al., 2003) with boundaries from the atlas of Tzourio-Mazoyer and colleagues (Tzourio-Mazoyer et al., 2002) with a significance level of $P < 0.05$, small volume corrected for family-wise error. The amygdala search volume comprised 81 2mmvoxels (approximately 0.65 cm) on each side (left, right) and the OMPFC search volume comprised 6176 2mmvoxels (approximately 49.4 cm).

Table 1
Mean (SD) accuracy of Ekman facial emotion valence identification as a function of emotion and IED status.

Variable	IED ($N = 20$)	HC ($N = 20$)	*t*
Neutral	0.90 (0.10)	0.92 (0.12)	0.43
Happy	0.99 (0.04)	0.97 (0.05)	1.23
Angry	0.75 (0.21)	0.83 (0.12)	1.40

Note: all *t* values = $P > 0.22$; IED = Intermittent Explosive Disorder; HC = Healthy Control subjects.

3. Results

3.1. Behavioral

IED and HC subjects did not differ in their ability to correctly identify angry, neutral and happy facial expressions (see Table 1).

3.2. Imaging

3.2.1. ROI analysis

IED subjects showed greater right amygdala activation in response to angry faces as compared to healthy controls (Z = 2.36; cluster size = 20; MNI = 24, 2, −22; $P < 0.05$ corrected for the amygdala volume); Fig. 1a. IED and control subjects did not differ in amygdala activation to the happy facial expression. IED and control subjects also failed to differ in OMPFC activation to angry (or happy) faces (all $P > 0.26$).

To confirm group differences in right amygdala activation, we conducted 2-sample *t*-tests of parameter estimates of activation extracted from a 10 mm sphere surrounding peak activation (β weights, arbitrary units [a.u.]), an index of BOLD signal change (BSC) using MarsBaR software (http://marsbar.sourceforge.net). Results again showed that IED subjects evidenced greater activation to angry faces than controls, $t\ (38) = 2.21$, $P < 0.05$, Cohen's $d = 0.70$ (Fig. 1b).

Secondary ROI analyses assessed whether habituation (decrement in signal over time) differed between IED and control subjects. We examined parameter estimates of activation (β weights) to angry (vs. neutral) faces from the amygdala ROI between early (first 2 blocks) and late (second 2 blocks) phases of the imaging session. These estimates were entered into repeated measures ANOVA with time (early, late) and group (IED, HC) as factors. We observed significant main effects of time ($F[1,38] = 5.91$, $P = 0.02$) and group ($F[1,38] = 4.89$, $P = 0.03$) as well as a significant time × group interaction ($F[1,38] = 5.98$, $P = 0.02$). Follow-up *t*-tests showed that the interaction was driven by an increase in amygdala activation from early blocks to later blocks in the IED group (β IED early: $M = 0.01$, $SD = 0.62$; IED late: $M = 1.10$, $SD = 1.23$), $t(19) = 3.054$, $P < 0.01$, with no corresponding change in amygdala activation across blocks in the HC group (β HC early: $M = 0.03$ $SD = 0.47$; HC late: $M = 0.03$, $SD = 1.21$); $t(19) = 0.013$, $P = 0.99$. These data suggest that amygdala habituation to angry faces did not occur in either group, but that sensitization occurred among the IED group.

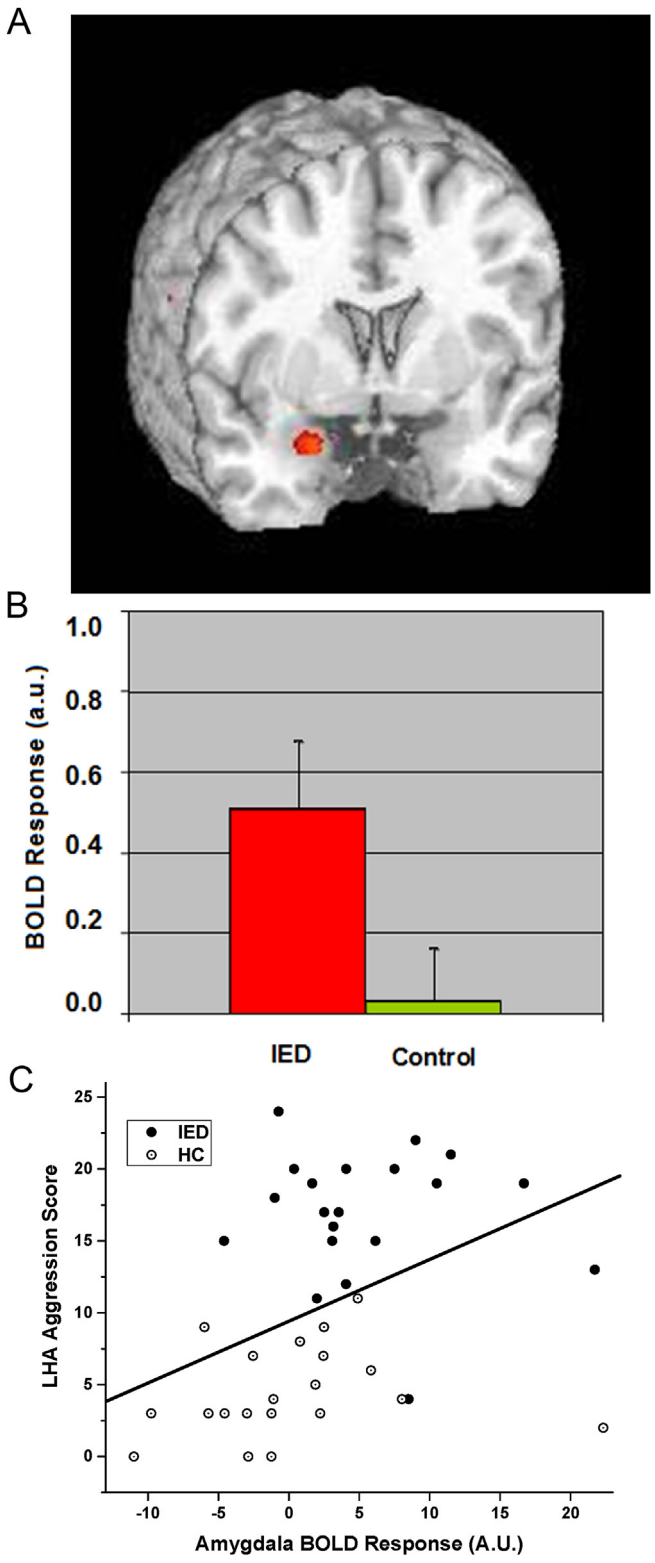

Fig. 1. Right amygdala response to angry facial expressions as a function of group. **(A)** statistical parametric *t*-map showing greater right amygdala activation to angry faces (vs. neutral faces) in IED as compared to healthy controls based on anatomically-derived ROI analysis (thresholded at $P < 0.05$ SVC); **(B)** Box plot of extracted parameter estimates of activation for angry (vs. neutral) facial expressions (β weights of BOLD Response, arbitrary units [a.u.]) from the right amygdala ROI showing significantly greater amygdala reactivity in IED (vs. NC) subjects only to angry faces (*$P < 0.05$). 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. **(C)** Correlation between life history of aggressive acts (i.e., LHA aggression score) and right amygdala BOLD response to angry faces (vs. neutral faces).

3.2.2. Aggression severity correlations

As group differences were found between IED and HC groups, secondary analyses examined whether lifetime frequency of aggressive acts (LHA Aggression scores) correlated directly with extracted amygdala BOLD response (β weights) to anger faces in the whole sample (rho = 0.45, $p < 0.005$; Fig. 1c). This correlation was similar, but non-significant, in HC subjects (rho = 0.36, p = 0.12), though nearly zero in IED subjects (rho = 0.04, p = 0.88), likely due to restriction of range in both groups.

3.2.3. Whole brain analysis

There were no other areas of hyperactivity for IED subjects (IED > HC) in response to the other facial emotions (all $Z < 2.08$). However, angry emotional faces resulted in hypoactivity for IED subjects in portions of the cerebellum and basal ganglia. Angry faces also produced less parahippocampal activation in IED as compared to control subjects (see Table 2). Regions that were active within each group individually (IED, HC) are reported in Table 3.

3.2.4. Functional connectivity

To assess OMPFC-amygdala functional connectivity we conducted a context-modulated psychophysiological interaction (PPI) analysis, assessing connectivity during angry face viewing relative to neutral, using averaged right amygdala time series as the seed (given its significantly altered activation reported above). We observed a significant difference in amygdala and frontal coupling between groups localized to the OMPFC ([−12 42 −6], Z = 3.75, $P < 0.005$, Fig. 2). Follow-up within group analyses showed that the HC subjects exhibited significant negative (e.g., reciprocal) amygdala-OMPFC coupling ([−10 42 −6], Z = 2.62, P < 0.005), in contrast to the IED subjects who showed a *positive* amygdala-OMPFC coupling ([−12 38 −6], Z = 3.26, $P < 0.005$). These data are highly consistent with our prior investigation that showed that IED subjects failed to exhibit a pattern of reciprocal (e.g., inverse) coupling between amygdala and OMPFC that was present in the HC group. (Coccaro et al., 2007).

4. Discussion

The increased right amygdala response to angry faces found among IED subjects (and aggressive behavior overall) is consistent with studies showing amygdala hyperactivity to negative emotional stimuli among emotionally dysregulated clinical populations (Fonzo et al., 2015; Thomas et al., 2013). This replicates and extends earlier research on IED (Coccaro et al., 2007) to an explicit facial emotion processing task. Thus, the current findings, along with our other findings of functional (Coccaro et al., 2007) and structural (Coccaro et al., 2016) amygdala deficits suggest that IED subjects demonstrate amygdala hyper-responsivity for angry faces that occurs independent of the centrality of emotion identification to the task response.

The current findings also tentatively argue for a neurofunctional dissociation between two disorders associated with aggression and increased risk of criminal behavior: IED and Psychopathy. Subjects with IED, a disorder of affective (a.k.a., hostile or impulsive) aggression, display increased amygdala response to emotional stimuli, which is consistent with the conceptualization of IED as a disorder of emotional dysregulation. In contrast, subjects with psychopathy, a disorder associated with instrumental (a.k.a., callous or unemotional) aggression, display amygdala hypoactivity to emotional stimuli (Marsh et al., 2008), which is consistent with

Table 2
Brain regions showing greater activation in HC (>IED) subjects in response to angry and happy facial expressions (relative to neutral): whole-brain voxel-wise analysis.

Emotion	Region	Side	MNI coordinates			Cluster size	Z score[a]
			x	y	z		
Angry	Parahippocampal Gyrus	L	−18	−24	−20	63	3.87
	Putamen	R	24	−10	18	23	3.59
	Culmen	R	6	−38	−24	20	3.36
Happy	No Significant Activations						

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 $P < .001$ uncorrected, clusters >10 contiguous voxels.

Table 3
Brain regions showing greater activation in response to angry and happy facial expressions (relative to neutral): whole-brain voxel-wise analysis in each group.

Group	Emotion	Region	Side	MNI coordinates			Cluster size	Z score[a]
				x	y	z		
HC	Angry	Cerebellum	L	−30	−58	−26	111	3.93
		Cerebellum	R	30	−62	−26	228	3.75
		Cerebellum	L	−14	−56	−50	506	3.96
		Cerebellum	L	−28	−46	−50	16	3.39
		Posterior Cingulate	R	12	−42	24	544	4.19
		Precuneus	R	0	−84	44	172	3.83
		Caudate	R	24	−10	18	99	3.72
		Lingual Gyrus	L	−8	−74	−6	34	3.56
		Anterior Cingulate	R	16	24	20	24	3.55
		Temporal Pole	R	36	12	28	21	3.42
	Happy	No Significant Activations						
IED	Angry	**Amygdala**	**R**	**24**	**2**	**−22**	**53**	**3.07**[b]
		Thalamus	R	26	−26	6	46	3.99
		Middle Temporal Gyrus	R	46	−36	4	75	3.80
		Temporal Pole	R	44	16	−28	10	3.47
		Insula	R	26	22	−18	27	3.66
		Middle Frontal Gyrus	R	62	−50	−2	19	3.45
	Happy	No Significant Activations						

IED = Intermittent Explosive Disorder; HC = Healthy Control subjects; MNI = Montreal Neurological Institute; L = Left; R = Right.
[a] Z-scores and significance for non-bolded items based on based whole-brain voxel-wise $P < .001$ uncorrected, clusters >10 contiguous voxels.
[b] Area in bold represent an *a priori* region of interest significant at $P < .05$ for ROI volume.

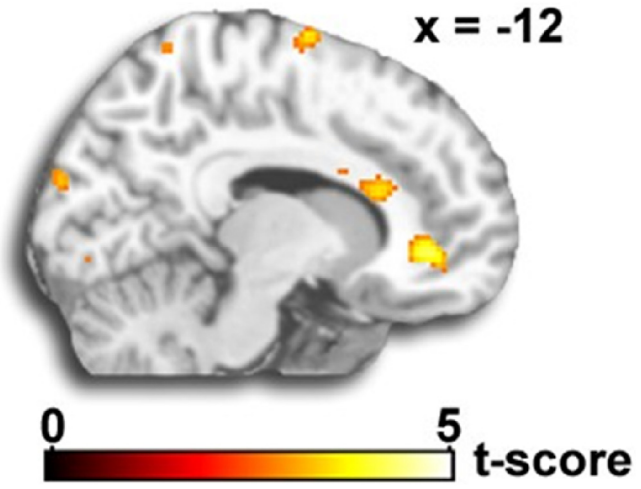

Fig. 2. Group (IED > HC) contrast of psychophysiological interaction (PPI) between amygdala and other brain regions (thresholded at $P < 0.005$ SVC).

data demonstrating reduced emotional response to threat and the negative consequences of acting on that threat (Birbaumer et al., 2005). In this context, it is important to note that IED subjects in our study had a mean PCL-SV score of 5.9 ($SD = 3.9$), well within the "non-psychopathic" range of 0–12 (Hart et al., 2003).

We failed to find diminished OMPFC reactivity to angry faces among IED subjects. This may simply be a type-II error[1] as previous research has shown OMPFC hypoactivity in aggressive clinical populations (Blair, 2008; Herpers et al., 2014; Huang et al., 2014; Schulze et al., 2011), including those with IED (Coccaro et al., 2007). Arguing against this is the fact that the current study sample was twice that of the earlier IED study and group differences in activation to angry faces in the OMPFC did not approach significance. However, in both studies there were a relatively low number of presentations of each emotion block, and it is possible that this limited our power to detect a significant effect.

Another possibility is that the task demands of the study (i.e., trying to identify facial affect) may have mitigated the tendency for OMPFC hypoactivity among IED subjects. This is consistent with research showing cognitive behavioral therapy, which in part increases awareness of socioemotional information processing, reduces aggression among subjects with IED (McCloskey et al., 2008). Other studies have shown that tasks involving facial expression identification result in lower limbic system and increased lateral and medial PFC activation relative to tasks requiring implicit emotion processing (Gyurak et al., 2011; Habel et al., 2007;

[1] Though we had sufficient power (>0.80) to detect a large effect of relative OMPFC hypoactivity in IED comparable to that found in Coccaro et al., 2007, our power to detect a more moderate effect (e.g. $d = 0.50$) was somewhat limited ($1-\beta = \sim 0.50$).

Lieberman et al., 2007). Thus, it is plausible that the explicit nature of the emotion processing task resulted in more PFC activation than the previously studied implicit emotion processing task. However, this study did not compare explicit and implicit emotion processing in IED, and although these forms of emotion processing have been compared in non-clinical samples, future studies directly comparing these processes between IED and control subjects are needed to properly evaluate this possibility.

Connectivity analysis showed reduced coupling between amygdala and OMPFC among IED (vs. control) subjects when processing angry faces, suggesting that the OMPFC may be less effective in dampening the amygdala response. This finding is in line with prior research (Coccaro et al., 2007) suggesting that, among individuals with IED, the OFC is less effective in regulating amygdala hyperactivity, while strong coupling exists between OFC and similar regions (e.g. ventral anterior cingulate cortex) in healthy individuals (e.g. Passamonti et al., 2009, 2012b). This dynamic system, in which the OFC and amygdala are interrelated, is important for emotion regulation and control of aggressive behaviors, and findings from this study add to existing evidence (Coccaro et al., 2011) suggesting that impairment of this circuitry may play a role in the neuropathophysiology of aggressive disorders.

Whole brain analysis found greater activation in the basal ganglia and cerebellum to angry faces for control (vs. IED) subjects. While most often associated with motor function, these regions are richly interconnected with multiple cortical areas that include the prefrontal cortex, where they aid in cognitive function including emotion recognition (Phan et al., 2004). Accordingly, hypoactivations in these regions could be due to differences between IED and HC subjects in motor cognitions related to anger detection.

Angry faces also resulted in greater activation for control subjects in the parahippocampal gyrus (PHG), possibly suggesting an increased focus on processing of the facial image and relating it as the PHG is associated with integrating perceptual memory for non-facial (Vuilleumier et al., 2001) and to a lesser extent facial (Haxby et al., 2001) stimuli. Increased activity in the PHG may also suggest greater recall of associative memories related to anger among control subjects, as the PHG is linked to retrieval of visually encoded memories (Takahashi et al., 2002).

IED and control subjects did not differ in their ability to identify angry or happy facial emotions. Previous research on facial emotion identification deficits in IED has been mixed (Best et al., 2002; Coccaro et al., 2007). All of the aforementioned studies used relatively small sample sizes and it may be that the Ekman facial identification task as administered is not sensitive enough to consistently pick up what may be subtle group differences, though other research studies have used faces of reduced, and/or varying, emotional intensity, which may more reliably identify facial emotion processing anomalies in clinical populations (Lynch et al., 2006).

IED subjects were not excluded for life history of other Axis I or II disorders, as this would have greatly impacted study feasibility and generalizability of the results, as IED has an over 80% co-morbidity rate with other psychological disorders (Kessler et al., 2006). Future studies may want to compare IED to controls matched for diagnostic comorbidity to further assess neural functioning pattern specific to IED. In addition, the task design involved five consecutive faces of the same emotion type, which may have produced strong expectations, further limiting the generalizability of the results; though the fMRI behavioral data showing only moderate accuracy [67%–86%] identifying facial emotion valence would argue against this. Finally, control subjects failed to show significant amygdala activation to emotional (relative to neutral) pictures. This is in contrast to most neuroimaging studies that show amygdala response to threatening pictures (Phan et al., 2004). This lack of a stronger amygdala signal may be associated with the expectancy effects mentioned above, which may have reduced stimuli novelty due to our repeated blocked fMRI design and consequently amygdala response due to habituation (Wright et al., 2003). It is also possible that the relatively low number of trial blocks (four per emotion) may have limited our ability to detect signal differences between emotion and neutral conditions. Increased repetitions of less predictable stimuli may have increased the contrast between angry/happy vs. neutral faces for healthy and IED subjects.

Accordingly, these issues limit the ability to draw definitive conclusions from the present study. Accordingly, future studies matching IED and control subjects across co-morbid disorders are needed to confirm (or modify) the study's findings. In addition, future studies investigating the endophenotypic nature of amygdala responses to anger faces may be performed by examining IED and non-IED unaffected siblings.

Even with these limitations, our results extend and modify previous research on socioemotional information processing among patients with IED, and provide insights into potential pharmacological and psychosocial treatment interventions for a disorder that currently has no empirically supported treatment. The finding of amygdala hyperactivity among IED patients argues for a pharmacological treatment that would reduce limbic activity. For example, selective serotonin reuptake inhibitors (SSRIs) have been shown to normalize amygdala function in IED (Coccaro et al., 2015), and in other clinical groups (Sheline et al., 2001), and to reduce aggressive behavior (Coccaro et al., 2009b). Further support for this idea comes from research findings in healthy adults suggesting that manipulating serotonin levels through acute tryptophan depletion modulates the connectivity between the amygdala and prefrontal cortex areas when processing angry faces (Passamonti et al., 2012b). The lack of an OMPFC deficit during explicit emotional identification in the present study may suggest that conscious effortful processing reduces prefrontal deficits associated with aggression, as interventions aimed at increased attention to perceptions and evaluations of socioemotional information to reduce aggressive behavior in IED (McCloskey et al., 2008).

Contributions

Mike McCloskey was involved in study design, analysis, interpretation, and manuscript writing. Luan Phan was involved in data analysis, interpretation and manuscript writing. Mike Angstadt was involved in data analysis and interpretation. Karla Fettich was involved in manuscript writing. Sarah Keedy was involved in results interpretation and manuscript writing. Emil Coccaro was involved in data analysis, interpretation, and manuscript writing.

Conflicts of interest/Financial disclosures

Dr. Coccaro reports being on the Scientific Advisory Board of Azevan Pharmaceuticals, Inc. Drs. McCloskey, Phan, and Keedy have nothing to disclose; Mr. Angstadt and Ms. Fettich have nothing to disclose. There are no conflicts of interest with any of the authors.

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