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Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: An event-related fMRI study

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Abstract

Clinical hallmarks of borderline personality disorder (BPD) include social and emotional dysregulation. We tested a model of fronto-limbic dysfunction in facial emotion processing in BPD. Groups of 12 unmedicated adults with BPD by DSM-IV and 12 demographically-matched healthy controls (HC) viewed facial expressions (Conditions) of neutral emotion, fear and anger, and made gender discriminations during rapid event-related functional magnetic resonance imaging (fMRI). Analysis of variance of Region of Interest signal change revealed a statistically significant effect of the Group-by-Region-by-Condition interaction. This was due to the BPD group exhibiting a significantly larger magnitude of deactivation (relative to HC) in the bilateral rostral/subgenual anterior cingulate cortex (ACC) to fear and in the left ACC to fear minus neutral; and significantly greater activation in the right amygdala to fear minus neutral. There were no significant between-group differences in ROI signal change in response to anger. In voxel-wise analyses constrained within these ROIs, the BPD group exhibited significant changes in the fear minus neutral contrast, with relatively less activation in the bilateral rostral/subgenual ACC, and greater activation in the right amygdala. In the anger minus neutral contrast this pattern was reversed, with the BPD group showing greater activation in the bilateral rostral/subgenual ACC and less activation in the bilateral amygdala. We conclude that adults with BPD exhibit changes in fronto-limbic activity in the processing of fear stimuli, with exaggerated amygdala response and impaired emotion-modulation of ACC activity. The neural substrates underlying processing of anger may also be altered. These changes may represent an expression of the volumetric and serotonergic deficits observed in these brain areas in BPD.

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1. Introduction

Borderline personality disorder (BPD) is a chronic, serious disorder characterized by interpersonal dysfunction, emotional instability and behavioral impulsivity (Lieb et al., 2004). The neurobiological basis of these first two symptom domains remains obscure. However,

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converging evidence suggests that the social and emotional disturbances of BPD may have a basis in the functional neuroanatomy of social/emotional information processing, supported by fronto-limbic circuitry (see reviews in [Brendel et al., 2005](#); [Schmahl and Bremner, 2006](#)).

BPD patients exhibit a number of changes in the structure and function of subcortical limbic areas. This includes volume loss and lower resting metabolism in the amygdala and hippocampus ([Driessen et al., 2000](#); [Juengling et al., 2003](#); [Rusch et al., 2003](#); [Schmahl et al., 2003a](#); [Tebartz van Elst et al., 2003](#); [Brambilla et al., 2004](#); [Irle et al., 2005](#)), though some studies have found amygdala volume to be preserved ([Zetzsche et al., 2006](#)). The functional effects of this limbic pathology include elevated amygdala responses to emotional stimuli ([Herpertz et al., 2001](#); [Donegan et al., 2003](#)) and episodic memory deficits ([Fertuck et al., 2006](#)) which may be due to intrinsic hippocampal pathology or secondary to amygdala hyperactivity ([Kim and Diamond, 2002](#)).

BPD patients also exhibit deficits in the structure and function of the rostral and subgenual subregions of the anterior cingulate cortex (ACC). This includes volume loss ([Tebartz van Elst et al., 2003](#)) and impaired *in vivo* serotonin synthesis ([Leyton et al., 2001](#)). Patients with major depressive disorder and comorbid BPD also exhibit impaired ACC metabolic response to fenfluramine in this region, relative to those without comorbid BPD ([Oquendo et al., 2005](#)). Other studies of subject samples that were comprised by a majority of BPD patients have found rostral and/or subgenual ACC deficits including impaired metabolic responses to fenfluramine ([Siever et al., 1999](#)) and m-chlorophenylpiperazine ([New et al., 2002](#)) and impaired serotonin transporter availability ([Frankle et al., 2005](#)). In addition, remediation of impulsive aggressive symptoms in BPD patients with 12-week fluoxetine treatment is correlated with increased blood flow in these ACC regions ([New et al., 2004](#)). BPD patients also appear to exhibit deficits in more dorsal subregions of ACC. This includes volume loss ([Hazlett et al., 2005](#)), greater metabolic deactivation in response to abandonment scripts, relative to healthy adults ([Schmahl et al., 2003b](#)), and greater deactivation during recall of traumatic memories, relative to traumatized subjects without BPD ([Schmahl et al., 2004](#)).

The ACC may be a key neural region where altered processing of social and emotional information is expressed in some of the hallmark clinical signs of this disorder. The ACC is necessary for the maternal separation distress call of infant squirrel monkeys

([MacLean and Newman, 1988](#)), and is activated in healthy adult humans both during the subjective experience of social rejection ([Eisenberger et al., 2003](#)) and during effortful control of subjective emotional responses ([Ochsner and Gross, 2005](#)). These experimental paradigms are related to clinical phenomena that are very characteristic of BPD, such as social attachment disturbance, rejection sensitivity and emotion dysregulation, respectively ([Lieb et al., 2004](#)).

Among categorical facial emotional expressions, fear and anger may be particularly relevant to the pathophysiology of BPD. Expressions of fear have great ethological significance ([Blair, 2003](#)) and activate the amygdala in a number of (though not all) brain imaging studies of healthy adults ([Breiter et al., 1996](#); [Phillips et al., 1997, 1998](#); [Whalen et al., 2001](#); [Williams et al., 2001](#); [Pessoa et al., 2002](#); [Surguladze et al., 2003](#); see [Murphy et al., 2003](#) for review). While BPD patients do not typically exhibit exaggerated fear responses *per se*, they do exhibit a variety of aversive behavioral responses, such as approach-avoidance conflicts manifest in interpersonal settings ([Melges and Swartz, 1989](#)), as well as a range of negative affect states ([Zanarini et al., 1998](#)), which are likely associated with amygdala activity ([LeDoux, 2000](#); [Davidson, 2002](#)). Despite the clinical importance of social and emotional dysregulation in BPD, only one reported study to date has examined regional brain activation to facial emotion in BPD ([Donegan et al., 2003](#)). This study found greater left amygdala activation to neutral and negative facial emotions among BPD patients, compared to a healthy control group. In addition, serotonergic agents can modulate the processing of facial fear ([Harmer et al., 2003, 2004](#); [Attenburrow et al., 2003](#)), suggesting that the serotonergic dysfunction found in BPD patients may have deleterious effects on social-emotional function. Exaggerated anger and hostility is also characteristic of BPD patients ([Hatitaskos et al., 1997](#)), and many of the studies of ACC dysfunction in BPD patients cited above included patients with significant interpersonal antagonism ([Siever et al., 1999](#); [New et al., 2002, 2004](#); [Hazlett et al., 2005](#); [Frankle et al., 2005](#); [Oquendo et al., 2005](#)). To our knowledge, the present study is the first to examine the neural response to facial expressions of anger in BPD.

In addition, the rostral/subgenual ACC subregions implicated in the studies cited above typically exhibit deactivation during the performance of cognitive tasks, such as the gender discrimination task employed here (reviewed in [Drevets and Raichle, 1998](#); [Gusnard and Raichle, 2001](#)). In paradigms where the task demand is fixed and the item content varied, the rostral/subgenual

ACC and adjacent ventromedial PFC exhibit lesser degrees of deactivation with emotional content of the items (Whalen et al., 1998; Goel and Dolan, 2003). Conversely, in paradigms which hold the item content fixed and vary the cognitive task demands, these regions also exhibit lesser deactivation with task demands that are explicitly emotional in nature, compared to non-emotional task demands (Gusnard et al., 2001; Northoff et al., 2004). These studies indicate that features of emotion processing, found either in the content of the items or in the cognitive operations performed on them, are observed to modulate the deactivation of rostral and subgenual ACC.

In the present study, we presented facial expressions of fear and anger in order to test the model of fronto-limbic dysfunction. We hypothesized that the BPD group would exhibit relatively greater activation in the amygdala compared to the healthy control group, to negatively-valenced facial expressions. In addition, we hypothesized that negatively-valenced emotion content would modulate the activity of the rostral/subgenual ACC differentially among BPD patients.

2. Methods

2.1. Subjects

This study was approved by the Mount Sinai School of Medicine Institutional Review Board, and all subjects underwent informed consent prior to participation in study procedures. The borderline personality disorder group (BPD) and Healthy Control (HC) group both consisted of 12 adults recruited from the community. All subjects who underwent scanning were included in the analysis. The BPD group was matched to the HC group on age ($30.3\% \pm 8$ versus 30.7 ± 10 years; $P=0.9$), sex (7 male, 5 female, versus 6 male, 6 female) and race (White, Black, Latino, Asian, Mixed race: 3, 1, 4, 3, 1 versus 3, 5, 2, 2, 0; $\chi^2=4.53$, $df=4$, $P=0.34$). The sex-ratio of our sample is somewhat atypical of that found in treatment settings; however, a recent review of the empirical literature suggests that the female predominance found in clinical settings is largely the result of sampling bias (Skodol and Bender, 2003). Our subjects were recruited from the community, providing a sample that is more representative of the full population of individuals with BPD, and obviating the effects of psychotropic medications on the experimental measures. All subjects were free of significant medical illness, including neurological illness and history of head injury. BPD subjects were also excluded if they had lifetime co-morbid diagnoses of a primary psychotic

disorder, bipolar affective disorder type I, or substance dependence. No subjects met substance abuse criteria within 6 months of study and all had a negative urine drug screen prior to their scan. No BPD subjects were in active treatment with psychiatric medication at study; seven had no lifetime history of psychiatric medication exposure, and the remaining five had discontinued medication for a period of 4 months to several years. All subjects underwent diagnostic assessment with the Structured Interview for DSM-IV Personality Disorders (SIDP) (Pfohl et al., 1989), and the Structured Clinical Interview for DSM-IV Axis I (SCID-I) (First et al., 1995), with a masters or doctoral-level SCID-trained diagnostician. Consensus diagnoses were arrived at with the assistance of an expert diagnostician. Concurrent comorbid psychiatric diagnoses in this sample included the following: obsessive-compulsive disorder ($n=1$), post-traumatic stress disorder ($n=1$), panic disorder ($n=1$); and among comorbid personality disorder diagnoses, paranoid ($n=6$), schizotypal ($n=1$), antisocial ($n=1$), narcissistic ($n=5$), histrionic ($n=1$), avoidant ($n=4$).

2.2. Cognitive paradigm

Digitized stimuli from the Pictures of Facial Affect set (Ekman and Friesen, 1976) were used. These gray scale stimuli were modified by standardization of image intensity across the set and removal of hair and clothing from the images so that only the face remained in the image (Blair et al., 2001). From this modified set, faces expressing Fear, Anger and Neutral emotion (each with $>87\%$ consensus on normative emotion category ratings by the original Ekman and Friesen set) were chosen from each of eight models (four female and four male). Each subject performed four runs, with each run 288 s long containing 36 trials that comprised 12 Fear, 12 Anger and 12 Neutral faces, presented in pseudo-random order with a jittered intertrial interval, which was 6 s on average. At the beginning and end of each run, the fixation cross was presented for 36 s. Individual trials consisted of a single stimulus presented for 0.5 s duration followed by a fixation cross. Stimuli were presented with EPrime software and back-projected with subjects viewing stimuli with a mirror. Subjects were instructed to attend to all images and to make right-handed button presses to discriminate the gender of the model, with equal emphasis on speed and accuracy. The final (fourth) run from one HC subject and one BPD subject was excluded from analysis due to low accuracy ($<60\%$), with confirmation on post-scan debriefing that these subjects were falling asleep during the run. All

other accuracies were very high (>90%) for all subjects in all runs (see Section 3). Behavioral performance measures included accuracy and reaction time (RT); no hypotheses were made regarding group differences in performance. Both accuracy and RT were evaluated with analysis of variance (ANOVA), with the factors Group (HC, BPD) and Condition (Neutral, Fear, Anger). In addition, bivariate Pearson product-moment coefficients were also computed between accuracy, RT, and Percent signal change in each ROI, for each condition (see below). These analyses were conducted in order to evaluate whether between-group differences in neural activity are associated with differential task performance.

2.3. Functional magnetic resonance imaging procedure

Scanning was conducted on a Siemens Allegra 3T scanner. Head movement was restricted with the use of expandable foam cushions positioned lateral to the subject's head, and headphones which also minimized scanner noise. An automated scout image was first acquired. Then a T2-weighted structural MRI scan was obtained with a field of view (FOV)=210 mm, TE=106 ms, TR=4500 ms, and 170° flip angle; a single volume was obtained with 42 slices in the axial plane, and each slice with voxel size 0.41 mm×0.41 mm×2.5 mm with 0.825 mm skip between slices. For the functional MRI scans, T2*-weighted single-shot gradient-echo echo planar imaging was used for measurement of blood oxygen-level dependent (BOLD) signal (Ogawa et al., 1990), with FOV=210 mm, TE=40 ms, TR=3000 ms, and 90° flip angle (96 volumes/run). 42 interleaved slices per volume were obtained in the axial plane, with voxel size 3.28×3.28×2.5 mm (and 0.825 mm skip).

2.4. Image processing and inferential testing

Statistical Parametric Mapping (SPM2; Wellcome Department of Imaging Neuroscience, University College, London) was used for preprocessing and inferential testing. All images were subjected to linear motion correction to the first brain volume obtained during EPI for each subject, slice timing correction, coregistration, spatial normalization to the Montreal Neurological Institute (MNI) template implemented in SPM2, and spatial smoothing with an 8 mm full-width-at-half-maximum isotropic Gaussian kernel. Subject head movement was less than 2 mm in any dimension within and between each run for all subjects, and no fMRI data required exclusion. The analysis proceeded by convolving a train of delta functions, representing individual trial events, with the basis function, which was a

canonical gamma hemodynamic response function fitted to the BOLD event-related signal. The General Linear Model was used for inferential tests, both on regions of interest (ROI) and as whole-brain voxel-wise comparisons.

2.5. Region-of-interest analyses of BOLD signal change

ROIs for the amygdala and ACC were defined anatomically (each bilaterally) using the MarsBaR toolbox in SPM2, which derives ROIs from the MNI single-subject template (Tzourio-Mazoyer et al., 2002). In this library of ROIs, the ACC is distinguished from a “Mid Cingulum” ROI, and is primarily comprised of the rostral and subgenual extent of the ACC, both anterior and inferior to the genu of the corpus callosum. Percent signal change (relative to the low-level baseline activity observed during viewing of the fixation cross) in the ROIs was estimated using the model described above, and extracted for each subject as the mean signal within each ROI for each condition, across the four runs. These values were then entered into an ANOVA with the following factors: Group (HC, BPD), Region (amygdala, ACC), Hemisphere (Right, Left) and Condition (Neutral, Fear, Anger). The threshold for statistical significance was set at $P<0.05$ two-tailed. Significant effects involving the Group factor were then followed up with t tests, comparing Group on individual ROIs both in individual conditions and in contrasts of emotion (fear or anger) minus neutral, with significance set at $P<0.05$ (one-tailed for directional hypotheses).

2.6. Voxel-wise group comparisons for emotion–neutral contrasts

Voxel-wise contrasts were conducted as follows. In the first level of analysis, within-subject contrasts (fear minus neutral and anger minus neutral) were examined by voxel-wise t test using a fixed-effects model. Contrast images for each subject were then entered into the second level, between-group analysis for each of the two contrasts, employing a random-effects model. Statistical parametric maps were generated for each between-group comparison for each contrast of interest, expressed as t statistics at each voxel. Given our *a priori* hypotheses regarding ACC and amygdala activity and our desire to supplement the ROI analyses, we constrained the voxel-wise inferential testing to the ROIs described above, using a statistical threshold of $P<0.05$ (two-tailed) with eight contiguous voxels and with individual MarsBaR ROIs used in small volume

correction for multiple comparisons, to identify regions with significant between-group differences.

3. Results

3.1. Behavioral performance

ANOVA of accuracy revealed no significant effects of either Group or Group-by-Condition interaction ($P > 0.7$). The mean accuracies were $97.8\% \pm 3.5\%$ for the HC group and $97.1\% \pm 5.1\%$ for the BPD group. The ANOVA of RT revealed a main effect of Group that approached significance ($F[2,21] = 4.22$, $P = 0.052$) but no effect of the Group-by-Condition interaction ($P = 0.7$). The overall mean RT was 708 ± 130 ms for the HC group and 841 ± 149 ms for the BPD group. The bivariate correlations between accuracy, RT and Percent signal change in each ROI showed no significant correlations between any measures, in any of the three conditions (all $P > 0.10$).

3.2. Region-of-interest analyses of BOLD signal change

ANOVA revealed a statistically significant effect of the Group-by-Region-by-Condition interaction ($F[2,21] = 3.63$, $P = 0.044$) on ROI signal change. The main effect of Region was also significant ($F[1,22] = 16.58$, $P = 0.001$) and the effect of the Group-by-Region interaction term approached significance ($F[1,22] = 3.77$, $P = 0.065$). No other effects in the ANOVA approached significance. *Post-hoc* *t* tests showed the BPD group to exhibit a significantly greater decrease in signal change (relative to HC) in the ACC bilaterally to fear (Right ACC: $t = -2.42$, $df = 22$, $P = 0.012$; Left ACC: $t = -2.52$, $df = 22$, $P = 0.010$), and a trend toward greater increase in signal change (relative to HC) in the right amygdala to fear ($t = 1.67$, $df = 22$, $P = 0.055$) (Fig. 1). In *t* tests comparing the contrast of fear minus neutral faces, the BPD group showed a significantly greater decrease (relative to HC) in left ACC ($t = -1.78$, $df = 22$, $P = 0.045$) and a trend toward a significantly greater decrease (relative to HC) in the right ACC ($t = -1.47$, $df = 22$, $P = 0.078$). The direction of activity was different for the two groups in this contrast: the HC group showed lesser deactivation in signal to fear, whereas the BPD group showed greater deactivation to fear (Fig. 1). These effects were very similar between the ACC ROIs in each hemisphere (Fig. 1). The BPD group also exhibited a significantly greater increase in signal change in the fear minus neutral contrast in the right amygdala ($t = 2.00$, $df = 22$, $P = 0.030$). No significant group differences in signal change were observed for

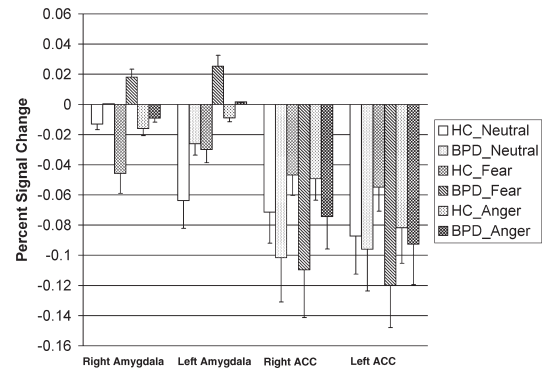


Fig. 1. Results of ROI analyses for BPD and HC groups. Histogram depicting percent signal change in each region of interest (ROI) for two subject groups in each facial emotion condition. Signal change was derived by fitting a canonical hemodynamic response function to the BOLD signal profile (using the General Linear Model), and extracted from ROIs defined from the MarsBaR library and implemented in SPM2. ACC: rostral/subgenual anterior cingulate cortex; HC: healthy control group; BPD: borderline personality disorder group.

neutral, anger or the anger minus neutral contrast in any ROI (all $P > 0.39$).

3.3. Voxel-wise group comparisons for emotion minus neutral contrasts

In the fear minus neutral contrast, the BPD group exhibited a significantly lesser activity, relative to the control group, in the bilateral rostral anterior cingulate gyrus (Table 1 and Fig. 2 middle image). One area of between-group difference in the ACC extended anterior and inferior from the maximum coordinate in the rostral ACC to the right medial frontal gyrus. Another large but more circumscribed area where the BPD group exhibited significantly lesser activity in the fear minus neutral contrast was observed in the right subgenual anterior cingulate gyrus (Table 1 and Fig. 2 middle image). The BPD group exhibited significantly greater activation in two clusters within the right amygdala (Table 1 and Fig. 2 top image). The larger of these two areas within the amygdala was found in the dorsal aspect, extending beyond the dorsal amygdala margin into the substantia innominata.

In the anger minus neutral contrast, while the HC group showed relatively large areas of activation in the amygdala bilaterally, the BPD group did not show any amygdala activation that exceeded threshold. This resulted in between-group comparisons showing the BPD group to exhibit relatively lesser activation in the amygdala bilaterally. This included areas in the right amygdala that were distinct from the loci of between-group differences in response to fear (Fig. 2 bottom

Table 1

Activation maxima for borderline personality disorder and healthy control groups

Region	BA	MNI coordinates			Voxels	Z	P
		x	y	z			
Fear minus neutral contrast							
<i>BPD</i>							
Left anterior cingulate gyrus	9/32	-14	42	14	10	2.61	.004
Right anterior cingulate gyrus	32	16	46	10	22	2.20	.014
<i>HC</i>							
Left anterior cingulate gyrus	24/32	-8	34	24	220	3.04	.001
	9	2	40	22		2.80	.003
	32	0	34	-6	21	2.33	.010
Right anterior cingulate gyrus	9/32	6	40	22	248	3.18	.001
	2	34	-6	13		2.26	.012
<i>BPD>HC</i>							
Right amygdala		22	-4	-12	13	2.04	.021
		34	-2	-28	8	2.54	.005
<i>HC>BPD</i>							
Left anterior cingulate gyrus	9	2	38	24	209	3.31	<.0005
	32/24	-6	34	26		3.02	.001
	32	0	36	-6	121	2.71	.003
	24	0	26	-2		2.18	.015
Right anterior cingulate gyrus	9/32	6	40	22	275	4.09	<.0005
	9	4	50	20		2.11	.017
	32	2	36	-6	28	2.58	.005
Neutral minus fear contrast							
<i>BPD</i>							
Left anterior cingulate gyrus	24	0	28	-6	33	2.80	.003
		0	26	-2		2.61	.004
	24/32	-2	28	24	35	2.08	.019
		2	26	20		1.95	.026
Right anterior cingulate gyrus	24	2	28	-6	28	3.04	.001
	24	4	26	20	13	1.96	.025
<i>HC</i>							
Right amygdala		24	0	-12	26	2.65	.004
Left anterior cingulate gyrus	24	-6	14	26	27	2.41	.008
<i>BPD>HC</i>							
Left anterior cingulate gyrus	24/32	0	32	-6	105	2.79	.003
		0	26	-2		2.52	.006
	9/32	2	42	22	138	2.56	.005
		-6	34	26		2.30	.011
	9/32	6	40	22	117	3.07	.001
		4	50	18		1.77	.039
	24	4	28	-4	62	2.75	.003
	24/32	2	32	-6		2.70	.003
<i>HC>BPD</i>							
Right amygdala		24	-2	-12	38	2.42	.008

Table 1 (continued)

Region	BA	MNI coordinates			Voxels	Z	P
		x	y	z			
<i>HC</i>							
Left amygdala		-28	-6	-12	92	3.23	.001
		-22	-6	-16		2.93	.002
		-30	2	-22		2.15	.016
Right amygdala		32	-4	-14	23	2.38	.009
		32	-4	-20		1.93	.027
Left anterior cingulate gyrus	24/32	-12	32	24	53	2.88	.002
Right anterior cingulate gyrus	24/32	16	30	24	332	3.59	<.0005
	32	6	36	-2		3.05	.001
	32	16	40	2		2.87	.002
	32/9	14	40	24		2.75	.003
	24/32	14	34	6		2.34	.010
		6	40	22		2.08	.019
		14	22	26		1.93	.027
<i>BPD</i>							
Left anterior cingulate gyrus	9	-14	42	41	66	2.75	.003
	9/32	-8	38	18		2.10	.018
	32	-14	32	28		1.76	.039
	24/32	-14	34	24		1.74	.041
Right anterior cingulate gyrus	24/32	12	34	18	206	2.25	.012
		16	28	24		2.16	.015
		10	32	28		2.06	.020
	32	18	44	8		1.90	.028
<i>BPD>HC</i>							
Left anterior cingulate gyrus	24	0	0	30	11	3.08	.001
	9/32	-8	38	18	12	1.84	.033
Right anterior cingulate gyrus	24	2	4	28	15	1.98	.024
		4	14	28		1.74	.041
<i>HC>BPD</i>							
Left amygdala		-28	-4	-12	11	2.02	.022
Right amygdala		32	0	-16	30	2.68	.004
		28	-8	-14		2.50	.006
Neutral minus anger contrast							
<i>BPD</i>							
(No significant activations)							
<i>HC</i>							
Right anterior cingulate gyrus	24	0	12	28	34	2.55	.005
		-4	4	30		2.30	.011
<i>BPD>HC</i>							
Left anterior cingulate gyrus	24	0	28	0	11	2.16	.015
<i>HC>BPD</i>							
(No significant activations)							

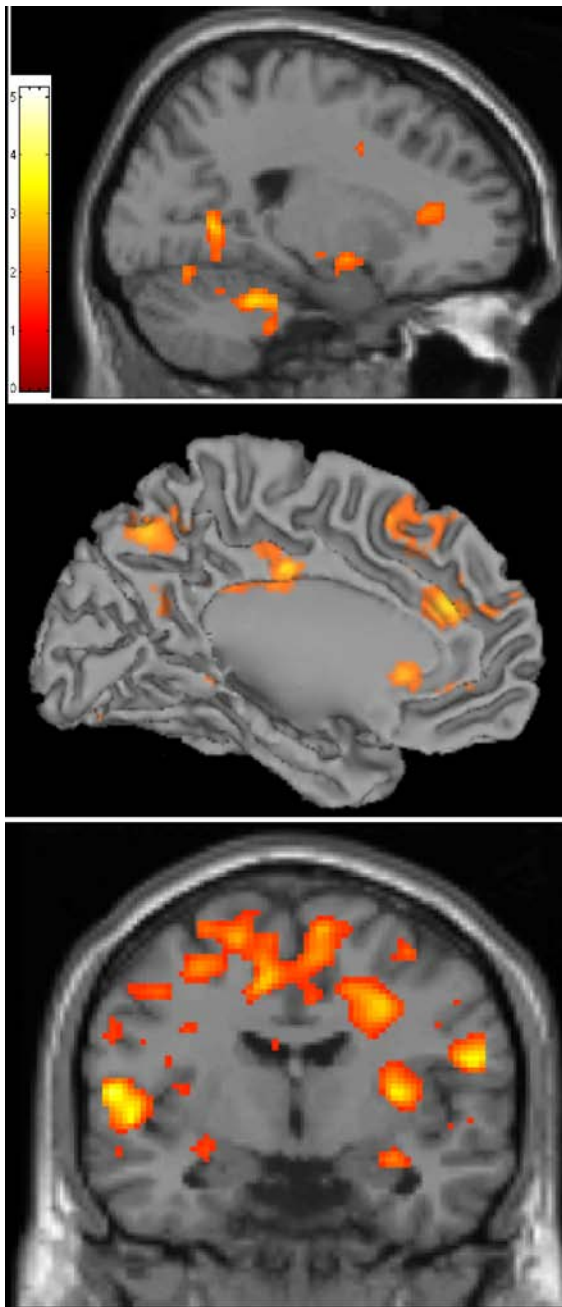


Fig. 2. Statistical parametric maps of between-group contrasts for emotion minus neutral. Top image: relative increase in right amygdala activation in BPD group compared to Healthy Control group on fear minus neutral contrast. Middle image: relative impairment in rostral/subgenual anterior cingulate cortex activation in BPD group compared to Healthy Control group on fear minus neutral contrast. Bottom image: relative increase in bilateral amygdala and dorsal ACC activation in BPD group compared to Healthy Control group on anger minus neutral contrast. Areas of activation are single-voxel color-coded t statistics with maximum = 5.0. Image orientations with right sagittal views and in neurological convention.

image). On the other hand, the BPD group showed significantly greater activity in multiple areas within the bilateral rostral ACC in the anger minus neutral contrast (Table 1 and Fig. 2 bottom image). These areas of the ACC were generally located considerably more posteriorly (more rostral than subgenual ACC) compared to those ACC subregions where the HC group showed relatively greater activity in the fear minus neutral contrast.

4. Discussion

The findings of this study provide support for the model of fronto-limbic dysfunction in BPD. This model posits that BPD patients exhibit a combination of limbic hyper-responsivity to social-emotional stimuli with an impaired response of PFC areas, particularly the ACC (Brendel et al., 2005; Schmahl and Bremner, 2006). Consistent with this notion, we found the amygdala to exhibit greater hemodynamic activation, and several subregions of ACC to exhibit impaired responses, to facial expressions of fear.

This sample of unmedicated adults with BPD exhibited increased activity in the right amygdala relative to the HC group, in response to facial expressions of fear. This group difference appeared to be related to the emotional content of the facial expressions, as the effect size was greater for the contrast of fear *versus* neutral faces, relative to that for fear faces alone. These group differences were not related to differential task performance, as the accuracy was neither different between groups nor related to BOLD signal changes in any condition. These findings are consistent with previous reports of increased amygdala response to emotional stimuli, including aversive pictures (Herpertz et al., 2001) and negatively-valenced facial expressions (Donegan et al., 2003).

A greater response to fear was also found in the region of the right amygdala among the BPD group compared to HC in the whole-brain analyses. This included one area within the amygdala proper, and another, larger area on the dorsal margin of the right amygdala, extending both inferiorly to the dorsal amygdala proper and superiorly into the substantia innominata (SI). This result suggests a measure of anatomical specificity of dysfunction within the so-called “extended” amygdala. Activation of these two subregions of the extended amygdala has been found in a number of studies using facial expressions of fear (Breiter et al., 1996; Phillips et al., 1997; Whalen et al., 1998, 2001; Morris et al., 2002; Pessoa et al., 2002). Areas of activation found in the more dorsal aspect of the amygdala may represent activity in the central nucleus,

which has been suggested to mediate bottom-up attention-modulating effects of emotional stimuli (Whalen et al., 1998, 2001) and the expression of fear-conditioned responses (Phelps and LeDoux, 2005). The activation extending into the SI may also mediate attention-modulating effects. The SI contains several forebrain cholinergic nuclei (Heimer, 2003) which can be driven by amygdala output (Alheid, 2003) and exert widespread effects on arousal and attentional processes throughout the cortex (Sarter et al., 2005). This suggests that heightened amygdala reactivity to social-emotional stimuli may have widespread deleterious effects on cortical attention-dependent processes in BPD. In addition, this amygdala reactivity may affect conditioned aversive responses, and thus form part of the basis for the approach-avoidance conflicts manifest in interpersonal settings, which are a clinical hallmark of BPD patients (Melges and Swartz, 1989).

In addition, the increased amygdala activity in the BPD group found in the voxel-wise analysis was lateralized to the right hemisphere. This finding was not hypothesized *a priori*. However, in the ANOVA of signal change in the ROIs, there was no statistically significant effect of Hemisphere in interaction with any other factor. Therefore, the possibility of lateralized effects of group differences in amygdala activation remains equivocal. This is consistent with a recent meta-analysis of fifty-four amygdala functional activation studies, which failed to support each of several possible information-processing functions of lateralized amygdala activity that have been proposed in the functional imaging literature (Baas et al., 2004).

In contrast to the increased amygdala activity found in the BPD group, this group exhibited impaired fear-modulation of task-related deactivation in ACC subregions. This is consistent with the findings of pathology in various subregions of the ACC among BPD patients, particularly in rostral and subgenual subregions (Siever et al., 1999; Leyton et al., 2001; New et al., 2002, 2004; Tebartz van Elst et al., 2003; Schmahl et al., 2003b, 2004; Hazlett et al., 2005; Frankle et al., 2005; Oquendo et al., 2005). While the functional status of dorsal ACC areas has been studied using script-driven hemodynamic responses, also finding greater deactivation in the BPD patients (Schmahl et al., 2003b, 2004), information-processing in the rostral or subgenual ACC has not previously been evaluated in BPD patients. We utilized the phenomenon of task-related deactivation, which is well-established in the rostral and subgenual ACC, to evaluate information processing in these ACC areas. The neural basis for this phenomenon remains unclear, though it may reflect a local decrease in

neural activity (Nair, 2005). This phenomenon is sensitive to emotion-modulation (Whalen et al., 1998; Gusnard et al., 2001; Goel and Dolan, 2003; Northoff et al., 2004), and we took advantage of this observation to evaluate the effects of facial emotion content on the activity of these ACC areas in BPD patients. We found the HC group to exhibit a tendency toward lesser deactivation in response to fear (compared to neutral faces), consistent with previous reports of modulatory effects of item emotion content (Whalen et al., 1998; Goel and Dolan, 2003). In contrast, the BPD group exhibited an impaired fear-modulatory effect, with a tendency toward the opposite direction (*i.e.* to further deactivation). An earlier empirical literature employed positron emission tomography (PET) to show that subgenual ACC deactivation is related to the attentional demands of visual tasks (Drevets and Raichle, 1998). This proposal has also found support in a more recent fMRI study that studied the effect on task-related deactivation of parametric variation of three attentional factors (McKiernan et al., 2003). This work suggests that in the present study, among BPD patients, the emotion content in facial expressions failed to facilitate attention-dependent task demands to the same degree as in healthy control subjects.

The voxel-wise contrast analyses indicated that the loci of significant impairments in the BPD group responses to fear were relatively circumscribed. This included areas in the rostral and subgenual ACC. These subregions are contained in the regions defined as ACC in the studies of impaired serotonergic activity among BPD patients (Siever et al., 1999; New et al., 2002, 2004; Frankle et al., 2005; Oquendo et al., 2005). Double-blind, placebo-controlled studies indicate that serotonergic agents can modulate healthy adults' ability to recognize facial expressions of fear (Harmer et al., 2003, 2004; Attenburrow et al., 2003). In addition, the degree of enhancement of subgenual ACC metabolic rate in response to SSRI treatment is highly correlated with remediation of aggression in BPD (New et al., 2004). Furthermore, in fear conditioning of healthy adults, the degree of attenuation of subgenual ACC deactivation to a previously-conditioned stimulus is associated with the degree of extinction of the conditioned skin conductance response (Phelps et al., 2004). In light of these findings, the present results may provide a link between local ACC serotonergic dysfunction and the aversive and antagonistic social interactions that are a clinical hallmark of BPD. This intriguing hypothesis may be tested in the future by administration of serotonergic agents while subjects perform ACC-focused emotion-processing tasks during fMRI.

We also found that in the voxel-wise analysis of anger minus neutral faces, the BPD group exhibited relatively *lesser* activation in the amygdala together with *greater* activation in the ACC. These results were not predicted in advance, and may appear counterintuitive, yet they appeared to be generally consistent with the direction of effects in the ROI analysis of responses to anger relative to neutral faces (see Fig. 1). Interestingly, the group differences in this contrast were found bilaterally in the amygdala (as were the within-control group activations to anger), and the areas of ACC where BPD subjects showed greater activation to anger were generally more posterior to that for fear. This finding is somewhat equivocal since significant group differences were not found for responses to anger in the ROI analysis. However, voxel-wise analyses can be informative as a more spatially-precise means of evaluating an anatomically and functionally heterogeneous brain region (such as the amygdala), compared to ROI measures which are summary measures for signal change across all voxels in a given ROI. Remarkably, neural responses to facial expressions of anger have not been studied to date in BPD patients, despite the clinical importance of hostility and interpersonal antagonism in this disorder (Hatzitaskos et al., 1997; Lieb et al., 2004). While the significance of the present finding remains unclear, it intriguingly suggests that there may be a dissociation between limbic processing of expressions of fear *versus* anger among BPD patients, which are generally conceived of as withdrawal-related *versus* approach-related emotions, respectively (Davidson, 2002). This dissociation could in turn be related to the co-occurrence of both aversive and antagonistic subjective states and behaviors among BPD patients. For example, anger expressed by others normally functions as a strong negative reinforcer of ongoing behavior (Blair, 2003), and perhaps the relative hypo-responsivity of the amygdala to these signals is related to an inability of BPD patients to manage socially undesirable behavior in interpersonal settings, including their own expressions of antagonistic thoughts and behaviors. The role of altered processing of anger may be addressed in future studies by examining the moderating effect of facial anger on processes such as reversal learning, cognitive control and response inhibition in disorders of interpersonal antagonism such as BPD.

4.1. Study limitations

The sample size in this study was modest, though comparable to that of most functional imaging studies of psychiatric populations. The BPD subjects in this study were free of concurrent psychotropic medications or

current major psychiatric conditions that are often found comorbidly in BPD, such as current major depression or bipolar I disorder. However, they were assigned diagnoses of various comorbid personality disorders. It remains unclear what contribution these other personality disorders may have made to the experimental findings. This study also did not include a clinical comparison group; therefore, the diagnostic specificity of the observed findings is uncertain at present. Indeed, the findings of other investigators, of decreased midline PFC activity and increased amygdala activity, in several disorders related to BPD such as PTSD (Shin et al., 2004), depression (Mayberg et al., 1999) and substance abuse (London et al., 2004), suggest that this neurobiological phenomenon may either underlie the social-emotional disturbances that are common to these disorders, or alternatively, may represent a more unitary basis for the range of symptoms found in mood, anxiety and personality disorders. Resolution of this issue will require direct comparison of different clinical samples in brain imaging paradigms, or considerably larger sample sizes in order to permit multivariate analyses of the relative influence of diagnostic heterogeneity on information processing in this disorder.

In addition, the control group did not exhibit activation in response to fearful expressions that was significantly different from either neutral faces or the baseline. Facial expressions of fear are generally considered to be reliably associated with positive activation of the amygdala in imaging studies of healthy adults (Breiter et al., 1996; Phillips et al., 1997, 1998; Whalen et al., 2001; Williams et al., 2001; Pessoa et al., 2002; Surguladze et al., 2003). Nevertheless, a number of studies of healthy adults (some studied as comparison groups for clinical populations) have found no significant activation by fMRI within the amygdala during the explicit presentation of fearful faces, compared to either neutral faces or a low-level baseline (Sprengelmeyer et al., 1998; Phillips et al., 1999; Narumoto et al., 2000; Kesler-West et al., 2001; Lange et al., 2003; Nelson et al., 2003; Winston et al., 2003; McClure et al., 2004; Holt et al., 2006; Russell et al., 2007). In addition, Morris et al. (1998) found increasing intensity of fear to activate the amygdala (by PET) only at a liberal threshold of $P < 0.05$ uncorrected, and in another study (Morris et al., 2002) these investigators found the prototypical-fearful faces minus prototypical-neutral faces contrast to show activations in some amygdala subregions and deactivations in others (see Fig. 3b *versus* Fig. 4b). Furthermore, Bishop et al. (2004) interestingly found relative amygdala deactivations to fear minus neutral in some subjects as a function of low state anxiety (see Fig. 2). Among the two studies that evaluated amygdala

responses to negative emotional stimuli in BPD patients, each study showed failures to detect significant amygdala activation in the healthy control groups. One study (Donegan et al., 2003) study showed no above-threshold activation in the amygdala in the control group in whole-brain analyses, even for the fearful (Ekman) faces minus fixation contrast at $P < 0.005$. In the other study (Herpertz et al., 2001), the control group showed no areas of activation in the negative minus neutral contrast (of IAPS images) even with a fixed-effects analysis at $P < 0.05$. One important and poorly-addressed issue in this literature is that in many of the positive studies reporting relative increase in amygdala activity to fear minus neutral, the neutral minus baseline (or fear minus baseline) contrasts are not reported, leaving it unclear whether the relative activity changes may represent lesser degrees of deactivation, as reported presently. The sources of variability in amygdala response to fear remain somewhat unclear, but may include task-related factors such as the order, rate, duration and heterogeneity of stimuli presented; task demands (see Drevets and Raichle, 1998 for discussion); covert processing strategies such as reappraisal, which might diminish amygdala activity (Ochsner et al., 2002; Phan et al., 2005); and variability in the signal from neutral faces or low-level baseline conditions for comparison (Johnstone et al., 2005). Overall, the findings from the present study thus appear to be well within the range of findings from the amygdala imaging literature in healthy adults, and are consistent with the findings from the two prior studies of amygdala responses to negative emotion in BPD. Some of the above-mentioned factors that may be responsible for variation in amygdala response among healthy adults (e.g. reappraisal, variability in neural response to emotional stimuli) may be directly tested in future studies as a potential basis for facial emotion processing disturbances in BPD.

4.2. Conclusions

Adults with BPD exhibit alterations in fronto-limbic activity in response to facial expressions of fear, with exaggerated amygdala responses and attenuated fear-modulation of activity in ACC subregions. There is preliminary evidence for altered limbic processing of expressions of anger as well. These suggest information-processing dysfunctions that may represent an expression of the altered structure and serotonin-modulation of these areas in BPD. Future studies should aim to further characterize the disturbances in processing of facial emotion, and the relationship to symptomatology both within the BPD diagnostic category and across related disorders of social and emotional function.

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References

- Alheid, G.F., 2003. Extended amygdala and basal forebrain. *Annals of the New York Academy of Sciences* 985, 185–205.
- Attenburrow, M.J., Williams, C., Odontiadis, J., Reed, A., Powell, J., Cowen, P.J., Harmer, C.J., 2003. Acute administration of nutritionally sourced tryptophan increases fear recognition. *Psychopharmacology (Berl)* 169 (1), 104–107.
- Baas, D., Aleman, A., Kahn, R.S., 2004. Lateralization of amygdala activation: a systematic review of functional neuroimaging studies. *Brain Research Brain Research Reviews* 45 (2), 96–103.
- Bishop, S.J., Duncan, J., Lawrence, A.D., 2004. State anxiety modulation of the amygdala response to unattended threat-related stimuli. *Journal of Neuroscience* 24 (46), 10364–10368.
- Blair, R.J., 2003. Facial expressions, their communicatory functions and neuro-cognitive substrates. *Philosophical Transactions of the Royal Society of London B* 358, 561–572.
- Blair, R.J., Colledge, E., Murray, L., Mitchell, D.G., 2001. A selective impairment in the processing of sad and fearful expressions in children with psychopathic tendencies. *Journal of Abnormal Child Psychology* 29, 491–498.
- Brambilla, P., Soloff, P.H., Sala, M., Nicoletti, M.A., Keshavan, M.S., Soares, J.C., 2004. Anatomical MRI study of borderline personality disorder patients. *Psychiatry Research Neuroimaging* 131 (2), 125–133.
- Brendel, G.R., Stern, E., Silbersweig, D.A., 2005. Defining the neurocircuitry of borderline personality disorder: functional neuroimaging approaches. *Development and Psychopathology* 17, 1197–1206.
- Davidson, R.J., 2002. Anxiety and affective style: role of prefrontal cortex and amygdala. *Biological Psychiatry* 51 (1), 68–80.
- Drevets, W.C., Raichle, M.E., 1998. Reciprocal suppression of regional cerebral blood flow during emotional *versus* higher cognitive processes: implications for interactions between emotion and cognition. *Cognition and Emotion* 12 (3), 353–385.
- Donegan, N.H., Sanislow, C.A., Blumberg, H.P., Fulbright, R.K., Lacadie, C., Skudlarski, P., Gore, J.C., Olson, I.R., McGlashan, T.H., Wexler, B.E., 2003. Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. *Biological Psychiatry* 54, 1284–1293.
- Driessen, M., Herrmann, J., Stahl, K., Zwaan, M., Meier, S., Hill, A., Osterheider, M., Petersen, D., 2000. Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Archives of General Psychiatry* 57, 1115–1122.
- Eisenberger, N.I., Lieberman, M.D., Williams, K.D., 2003. Does rejection hurt? An fMRI study of social exclusion. *Science* 302 (5643), 290–292.
- Ekman, P., Friesen, W.V., 1976. *Pictures of Facial Affect*. Consulting Psychologists, Palo Alto.

- Fertuck, E.A., Lenzenweger, M.F., Clarkin, J.F., Hoermann, S., Stanley, B., 2006. Executive neurocognition, memory systems, and borderline personality disorder. *Clinical Psychology Review* 26 (3), 346–375.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., Benjamin, L.S., 1995. *User's Guide for the Structured Clinical Interview for DSM-IV Axis I (SCID-I)*. American Psychiatric Press, Washington, DC.
- Frankle, W.G., Lombardo, I., New, A.S., Goodman, M., Talbot, P.S., Huang, Y., Hwang, D.R., Slifstein, M., Curry, S., Abi-Dargham, A., Laruelle, M., Siever, L.J., 2005. Brain serotonin transporter distribution in subjects with impulsive aggressivity: a positron emission study with [¹¹C]McN 5652. *American Journal of Psychiatry* 162 (5), 915–923.
- Goel, V., Dolan, R.J., 2003. Reciprocal neural response within lateral and ventral medial prefrontal cortex during hot and cold reasoning. *NeuroImage* 20 (4), 2314–2321.
- Gusnard, D.A., Raichle, M.E., 2001. Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience* 2 (10), 685–694.
- Gusnard, D.A., Akbudak, E., Shulman, G.L., Raichle, M.E., 2001. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America* 98 (7), 4259–4264.
- Harmer, C.J., Bhagwagar, Z., Perrett, D.I., Vollm, B.A., Cowen, P.J., Goodwin, G.M., 2003. Acute SSRI administration affects the processing of social cues in healthy volunteers. *Neuropsychopharmacology* 28 (1), 148–152.
- Harmer, C.J., Shelley, N.C., Cowen, P.J., Goodwin, G.M., 2004. Increased positive *versus* negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *American Journal of Psychiatry* 161 (7), 1256–1263.
- Hatzitaskos, P.K., Soldatos, C.R., Sakkas, P.N., Stefanis, C.N., 1997. Discriminating borderline from antisocial personality disorder in male patients based on psychopathology patterns and type of hostility. *Journal of Nervous and Mental Disorders* 185 (7), 426–442.
- Hazlett, E.A., New, A.S., Newmark, R., Haznedar, M.M., Lo, J.N., Speiser, L.J., Chen, A.D., Mitropoulou, V., Minzenberg, M., Siever, L.J., Buchsbaum, M.S., 2005. Reduced anterior and posterior cingulate gray matter in borderline personality disorder. *Biological Psychiatry* 58 (8), 614–623.
- Heimer, L., 2003. The legacy of the silver methods and the new anatomy of the basal forebrain: implications for neuropsychiatry and drug abuse. *Scandinavian Journal of Psychology* 44 (3), 189–201.
- Herpertz, S.C., Dietrich, T.M., Wenning, B., Krings, T., Erberich, S.G., Willmes, K., Thron, A., Sass, H., 2001. Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. *Biological Psychiatry* 50, 292–298.
- Holt, D.J., Kunkel, L., Weiss, A.P., Goff, D.C., Wright, C.I., Shin, L.M., Rauch, S.L., Hootnick, J., Heckers, S., 2006. Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophrenia Research* 82 (2–3), 153–162.
- Irlé, E., Lange, C., Sachsse, U., 2005. Reduced size and abnormal asymmetry of parietal cortex in women with borderline personality disorder. *Biological Psychiatry* 57 (2), 173–182.
- Johnstone, T., Somerville, L.H., Alexander, A.L., Oakes, T.R., Davidson, R.J., Kalin, N.H., Whalen, P.J., 2005. Stability of amygdala BOLD response to fearful faces over multiple scan sessions. *NeuroImage* 25 (4), 1112–1123.
- Juengling, F.D., Schmahl, C., Heflinger, B., Ebert, D., Bremner, J.D., Gostomzyk, J., Bohus, M., Lieb, K., 2003. Positron emission tomography in female patients with borderline personality disorder. *Journal of Psychiatric Research* 37, 109–115.
- Kesler-West, M.L., Andersen, A.H., Smith, C.D., Avison, M.J., Davis, C.E., Kryscio, R.J., Blonder, L.X., 2001. Neural substrates of facial emotion processing using fMRI. *Brain Research* 11 (2), 213–226.
- Kim, J.J., Diamond, D.M., 2002. The stressed hippocampus: synaptic plasticity and lost memories. *Nature Reviews Neuroscience* 3, 453–462.
- Lange, K., Williams, L.M., Young, A.W., Bullmore, E.T., Brammer, M.J., Williams, S.C., Gray, J.A., Phillips, M.L., 2003. Task instructions modulate neural responses to fearful facial expressions. *Biological Psychiatry* 53 (3), 226–232.
- LeDoux, J., 2000. Emotion circuits in the brain. *Annual Review of Neuroscience* 23, 155–184.
- Leyton, M., Okazawa, H., Diksic, M., Paris, J., Rosa, P., Mzengeza, S., Young, S.N., Blier, P., Benkelfat, C., 2001. Brain regional alpha-[¹¹C]methyl-L-tryptophan trapping in impulsive subjects with borderline personality disorder. *American Journal of Psychiatry* 158 (5), 775–782.
- Lieb, K., Zanarini, M.C., Schmahl, C., Linehan, M.M., Bohus, M., 2004. Borderline personality disorder. *Lancet* 364 (9432), 453–461.
- London, E.D., Simon, S.L., Berman, S.M., Mandelkern, M.A., Lichtman, A.M., Bramen, J., Shinn, A.K., Miotto, K., Leam, J., Dong, Y., Matochik, J.A., Kurian, V., Newton, T., Woods, R., Rawson, R., Ling, W., 2004. Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. *Archives of General Psychiatry* 61 (1), 73–84.
- MacLean, P.D., Newman, J.D., 1988. Role of midline frontolimbic cortex in production of the isolation call of squirrel monkeys. *Brain Research* 450 (1–2), 111–123.
- Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin, R.K., Jerabek, P.A., Silva, J.A., Tekell, J.L., Martin, C.C., Lancaster, J.L., Fox, P.T., 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *American Journal of Psychiatry* 156 (5), 675–682.
- McClure, E.B., Monk, C.S., Nelson, E.E., Zarahn, E., Leibenluft, E., Bilder, R.M., Charney, D.S., Ernst, M., Pine, D.S., 2004. A developmental examination of gender differences in brain engagement during evaluation of threat. *Biological Psychiatry* 55 (11), 1047–1055.
- McKiernan, K.A., Kaufman, J.N., Kucera-Thompson, J., Binder, J.R., 2003. A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *Journal of Cognitive Neuroscience* 15 (3), 394–408.
- Melges, F.T., Swartz, M.S., 1989. Oscillations of attachment in borderline personality disorder. *American Journal of Psychiatry* 146, 1115–1120.
- Morris, J.S., Friston, K.J., Buchel, C., Frith, C.D., Young, A.W., Calder, A.J., Dolan, R.J., 1998. A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain* 121 (Pt. 1), 47–57.
- Morris, J.S., deBonis, M., Dolan, R.J., 2002. Human amygdala responses to fearful eyes. *NeuroImage* 17 (1), 214–222.
- Murphy, F.C., Nimmo-Smith, I., Lawrence, A.D., 2003. Functional neuroanatomy of emotions: a meta-analysis. *Cognitive Affective and Behavioral Neuroscience* 3 (3), 207–233.
- Nair, D.G., 2005. About being BOLD. *Brain Research Brain Research Reviews* 50 (2), 229–243.
- Narumoto, J., Yamada, H., Iidaka, T., Sadato, N., Fukui, K., Itoh, H., Yonekura, Y., 2000. Brain regions involved in verbal or non-verbal aspects of facial emotion recognition. *NeuroReport* 11 (11), 2571–2576.

- Nelson, E.E., McClure, E.B., Monk, C.S., Zarahn, E., Leibenluft, E., Pine, D.S., Ernst, M., 2003. Developmental differences in neuronal engagement during implicit encoding of emotional faces: an event-related fMRI study. *Journal of Child Psychology and Psychiatry* 44 (7), 1015–1024.
- New, A.S., Buchsbaum, M.S., Hazlett, E.A., Goodman, M., Koenigsberg, H.W., Lo, J., Iskander, L., Newmark, R., Brand, J., O'Flynn, K., Siever, L.J., 2004. Fluoxetine increases relative metabolic rate in prefrontal cortex in impulsive aggression. *Psychopharmacology (Berl)* 176 (3–4), 451–458.
- New, A.S., Hazlett, E.A., Buchsbaum, M.S., Goodman, M., Reynolds, D., Mitropoulou, V., Sprung, L., Shaw, R.B., Koenigsberg, H., Platholi, J., Silverman, J., Siever, L.J., 2002. Blunted prefrontal cortical 18fluorodeoxyglucose positron emission tomography response to meta-chlorophenylpiperazine in impulsive aggression. *Archives of General Psychiatry* 59 (7), 621–629.
- Northoff, G., Heinzl, A., Bermpohl, F., Niese, R., Pfennig, A., Pascual-Leone, A., Schlaug, G., 2004. Reciprocal modulation and attenuation in the prefrontal cortex: an fMRI study on emotional–cognitive interaction. *Human Brain Mapping* 21 (3), 202–212.
- Ochsner, K.N., Gross, J.J., 2005. The cognitive control of emotion. *Trends in Cognitive Sciences* 9 (5), 242–249.
- Ochsner, K.N., Bunge, S.A., Gross, J.J., Gabrieli, J.D., 2002. Rethinking feelings: an fMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience* 14, 1215–1229.
- Ogawa, S., Lee, T.M., Kay, A.R., Tank, D.W., 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America* 87 (24), 9868–9872.
- Oquendo, M.A., Kronic, A., Parsey, R.V., Milak, M., Malone, K.M., Anderson, A., van Heertum, R.L., Mann, J.J., 2005. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge in major depressive disorder with and without borderline personality disorder. *Neuropsychopharmacology* 30 (6), 1163–1172.
- Pessoa, L., McKenna, M., Gutierrez, E., Ungerleider, L.G., 2002. Neural processing of emotional faces requires attention. *Proceedings of the National Academy of Sciences of the United States of America* 99 (17), 11458–11463.
- Pfohl, B.M., Blum, N., Zimmerman, M., Stangl, D., 1989. Structured Interview for DSM-III-R Personality: SIDP-R. Author, Iowa City, IA.
- Phan, K.L., Fitzgerald, D.A., Nathan, P.J., Moore, G.J., Uhdde, T.W., Tancer, M.E., 2005. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. *Biological Psychiatry* 57, 210–219.
- Phelps, E.A., LeDoux, J.E., 2005. Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron* 48 (2), 175–187.
- Phelps, E.A., Delgado, M.R., Nearing, K.I., LeDoux, J.E., 2004. Extinction learning in humans: role of the amygdala and vmPFC. *Neuron* 43 (6), 897–905.
- Phillips, M.L., Young, A.W., Senior, C., Brammer, M., Andrew, C., Calder, A.J., Bullmore, E.T., Perrett, D.I., Rowland, D., Williams, S.C., Gray, J.A., David, A.S., 1997. A specific neural substrate for perceiving facial expressions of disgust. *Nature* 389 (6650), 495–498.
- Phillips, M.L., Young, A.W., Scott, S.K., Calder, A.J., Andrew, C., Giampietro, V., Williams, S.C.R., Bullmore, E.T., Brammer, M., Gray, J.A., 1998. Neural responses to facial and vocal expressions of fear and disgust. *Proceedings of the Royal Society of London Series B* 265, 1809–1817.
- Phillips, M.L., Williams, L., Senior, C., Bullmore, E.T., Brammer, M.J., Andrew, C., Williams, S.C., David, A.S., 1999. A differential neural response to threatening and non-threatening negative facial expressions in paranoid and non-paranoid schizophrenics. *Psychiatry Research* 92 (1), 11–31.
- Rusch, N., van Elst, L.T., Ludaescher, P., Wilke, M., Huppertz, H.J., Thiel, T., Schmah, C., Bohus, M., Lieb, K., Hesslinger, B., Hennig, J., Ebert, D., 2003. A voxel-based morphometric MRI study in female patients with borderline personality disorder. *NeuroImage* 20 (1), 385–392.
- Russell, T.A., Reynaud, E., Kucharska-Pietura, K., Ecker, C., Benson, P.J., Zelaya, F., Giampietro, V., Brammer, M., David, A., Phillips, M.L., 2007. Neural responses to dynamic expressions of fear in schizophrenia. *Neuropsychologia* 45 (1), 107–123.
- Sarter, M., Hasselmo, M.E., Bruno, J.P., Givens, B., 2005. Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. *Brain Research Brain Research Reviews* 48 (1), 98–111.
- Schmah, C., Bremner, J.D., 2006. Neuroimaging in borderline personality disorder. *Journal of Psychiatric Research* 40 (5), 419–427.
- Schmah, C.G., Vermetten, E., Elzinga, B.M., Bremner, J.D., 2003a. Magnetic resonance imaging of HPC and amygdala volume in women with childhood abuse and borderline personality disorder. *Psychiatry Research* 122 (3), 193–198.
- Schmah, C.G., Elzinga, B.M., Vermetten, E., Sanislow, C., McGlashan, T.H., Bremner, J.D., 2003b. Neural correlates of memories of abandonment in women with and without borderline personality disorder. *Biological Psychiatry* 54 (2), 142–151.
- Schmah, C.G., Vermetten, E., Elzinga, B.M., Bremner, J.D., 2004. A positron emission tomography study of memories of childhood abuse in borderline personality disorder. *Biological Psychiatry* 55 (7), 759–765.
- Shin, L.M., Wright, C.I., Cannistraro, P.A., Wedig, M.M., McMullin, K., Martis, B., Macklin, M.L., Lasko, N.B., Cavanaugh, S.R., Krangel, T.S., Orr, S.P., Pitman, R.K., Whalen, P.J., Rauch, S.L., 2004. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Archives of General Psychiatry* 62 (3), 273–281.
- Siever, L.J., Buchsbaum, M.S., New, A.S., Spiegel-Cohen, J., Wei, T., Hazlett, E.A., Sevin, E., Nunn, M., Mitropoulou, V., 1999. d,l-fenfluramine response in impulsive personality disorder assessed with [18F]fluorodeoxyglucose positron emission tomography. *Neuropsychopharmacology* 20 (5), 413–423.
- Skodol, A.E., Bender, D.S., 2003. Why are women diagnosed borderline more than men? *Psychiatric Quarterly* 72 (4), 349–360.
- Sprengelmeyer, R., Rausch, M., Eysel, U.T., Przuntek, H., 1998. Neural structures associated with recognition of facial expressions of basic emotions. *Proceedings of the Royal Society of London Series B* 265 (1409), 1927–1931.
- Surguladze, S.A., Brammer, M.J., Young, A.W., Andrew, C., Travis, M.J., Williams, S.C.R., Phillips, M.L., 2003. A preferential increase in the extrastriate response to signals of danger. *NeuroImage* 19, 1317–1328.
- Tebartz van Elst, L., Hesslinger, B., Thiel, T., Geiger, E., Haegele, K., Lemieux, L., Lieb, K., Bohus, M., Hennig, J., Ebert, D., 2003. Frontolimbic brain abnormalities in patients with borderline personality disorder: a volumetric magnetic resonance imaging study. *Biological Psychiatry* 54 (2), 163–171.
- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage* 15 (1), 273–289.

- Whalen, P.J., Rauch, S.L., Etcoff, N.L., McInerney, S.C., Lee, M.B., Jenike, M.A., 1998. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *Journal of Neuroscience* 18 (1), 411–418.
- Whalen, P.J., Shin, L.M., McInerney, S.C., Fischer, H., Wright, C.I., Rauch, S.L., 2001. A functional MRI study of human amygdala responses to facial expressions of fear *versus* anger. *Emotion* 1 (1), 70–83.
- Williams, L.M., Phillips, M.L., Brammer, M.J., Skerrett, D., Lagopoulos, J., Rennie, C., Bahramali, H., Olivieri, G., David, A.S., Peduto, A., Gordon, E., 2001. Arousal dissociates amygdala and hippocampal fear responses: evidence from simultaneous fMRI and skin conductance recording. *NeuroImage* 14, 1070–1079.
- Winston, J.S., O’Doherty, J., Dolan, R.J., 2003. Common and distinct neural responses during direct and incidental processing of multiple facial emotions. *NeuroImage* 20 (1), 84–97.
- Zanarini, M.C., Frankenburg, F.R., DeLuca, C.J., Hennen, J., Khera, G.S., Gunderson, J.G., 1998. The pain of being borderline: dysphoric states specific to borderline personality disorder. *Harvard Review of Psychiatry* 6 (4), 201–207.
- Zetzsche, T., Frodl, T., Preuss, U.W., Schmitt, G., Seifert, D., Leinsinger, G., Born, C., Reiser, M., Moller, H.J., Meisenzahl, E.M., 2006. Amygdala volume and depressive symptoms in patients with borderline personality disorder. *Biological Psychiatry* 60 (3), 302–310.