

## BRIEF REPORT

# Functional Imaging of Emotion Reactivity in Opiate-Dependent Borderline Personality Disorder

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Opiate dependence (OD) and borderline personality disorder (BPD), separately and together, are significant public health problems with poor treatment outcomes. BPD is associated with difficulties in emotion regulation, and brain-imaging studies in BPD individuals indicate differential activation in prefrontal cingulate cortices and their interactions with limbic regions. Likewise, a similar network is implicated in drug cue reactivity in substance abusers. The present, preliminary study used functional MRI to examine activation of this network in comorbid OD/BPD participants when engaged in an “oddball” task that required attention to a target in the context of emotionally negative distractors. Twelve male OD/BPD participants and 12 male healthy controls participated. All OD/BPD participants were taking the opiate replacement medication Suboxone, and a subset of participants was positive for substances of abuse on scan day. Relative to controls, OD/BPD participants demonstrated reduced activation to negative stimuli in the amygdala and anterior cingulate. Unlike previous studies that demonstrated hyperresponsivity in neural regions associated with affective processing in individuals with BPD versus healthy controls, comorbid OD/BPD participants were hyporesponsive to emotional cues. Future studies that also include BPD-only and OD-only groups are necessary to help clarify the individual and potentially synergistic effects of these two conditions.

*Keywords:* borderline personality disorder, opiate dependence, fMRI, amygdala, emotion

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Borderline personality disorder (BPD) is characterized by functional impairment across interpersonal, behavioral, cognitive, and especially emotional domains (Rosenthal et al., 2008; Skodol et al., 2002). In addition to difficulties associated with the disorder itself, BPD frequently co-occurs with Axis I disorders including substance dependence (Grant et al., 2008; Skodol et al., 2002). Comorbidity between opiate dependence (OD) and BPD is particularly problematic. Within treatment-seeking OD populations, comorbidity with BPD ranges from 5.2% (Brooner, King, Kidorf, Schmidt, & Bigelow, 1997) to 44% (Sansone, Whitecar, & Wiederman, 2008), and among individuals identified with BPD, approximately 38% meet criteria for drug abuse or dependence (Trull, Sher, Minks-Brown, Durbin, & Burr, 2000). Among those in treatment for OD, the presence of BPD is associated with poorer outcomes, including higher rates of mood disorder, heroin overdose, suicide, and injection-related health problems at follow-up (Darke et al., 2007; Kosten, Kosten, & Rounsaville, 1989). One potential contributor to the high rate of comorbidity between BPD and OD is a desire among BPD individuals to “self-medicate” as a way of coping with overwhelming negative affect (Trull et al., 2000). A greater understanding of affective processes that underlie comorbid OD/BPD has the potential to inform the understanding and treatment of this difficult condition.

Disruptions in affective processing have been observed in both BPD and OD. In BPD, studies using self-report and experience sampling techniques have demonstrated greater affective instability (Ebner-Priemer et al., 2007; Koenigsberg et al., 2002; Stein, 1996; Trull et al., 2008). Psychophysiological studies of emotion in BPD are mixed, with some studies suggesting heightened physiological reactivity to emotion (Ebner-Priemer et al., 2005, 2007) and others suggesting hypoarousal (Herpertz, Kunert, Schwenger, & Sass, 1999; Herpertz et al., 2000). In addition, individuals with BPD show heightened sensitivity to identification of emotional cues in laboratory studies (Domes et al., 2008; Lynch et al., 2006; Wagner & Linehan, 1999). In contrast to heightened sensitivity to emotion in BPD, OD individuals show impaired ability to identify facial expressions of emotion (Kornreich et al., 2003; polysubstance users including a high percentage of opiate users; Verdejo-

Garcia, Rivas-Perez, Vilar-Lopez, & Perez-Garcia, 2007). Although studies are inconsistent in reports of heightened or reduced subjective ratings of emotional cues relative to non-substance-using controls, OD individuals show an attenuated heart rate, blood pressure, and endocrine response to negative stimuli relative to controls (Gerra et al., 2003), anomalous zygomatic muscle reactivity to negative images (Lubman et al., 2009), and exaggerated attentional blink (i.e., a deficit in perceiving the second of two stimuli presented in close succession) to negative and neutral (but not addiction-related) stimuli following an initial stimulus (Liu, Li, Sun, & Ma, 2008). They also fail to demonstrate valence or arousal effects on attention as measured by P300 event-related potential responses to novel cues in positive, negative, and neutral emotional contexts (Marques-Teixeira & Santos Barbosa, 2005). These findings have led to the suggestion that substance-dependent individuals, including OD, demonstrate a reduced sensitivity to emotional stimuli (Verdejo-Garcia, Perez-Garcia, & Bechara, 2006). Given findings of emotion hypersensitivity in BPD and hyposensitivity in OD, it is unclear how emotion sensitivity may be affected in a comorbid population.

Consistent with behavioral and self-report studies, BPD is characterized by functional changes in brain regions serving emotional processes. BPD individuals show reduced ventromedial prefrontal activation, including orbitofrontal cortex, and increased limbic/striatal activation when engaging in a go/no-go task under emotional load, suggesting a neural link between emotion dysregulation and impulsive behavior (Silbersweig et al., 2007). Likewise, heightened activity in amygdala (Donegan et al., 2003; Driessen et al., 2004; Herpertz et al., 2001; Koenigsberg et al., 2009; Minzenberg, Fan, New, Tang, & Siever, 2007), medial prefrontal cortex (Herpertz et al., 2001; Schnell & Herpertz, 2007), and orbitofrontal cortex (Driessen et al., 2004) has been observed in BPD participants (relative to both healthy controls and non-BPD individuals with a history of trauma or abuse) when engaging with emotional stimuli. Disturbed connectivity between prefrontal regions (associated with emotion regulation and impulse control) and limbic regions including amygdala (associated with emotion reactivity) has been implicated in BPD (New et al., 2007). Overall, neu-

roimaging studies largely provide support for the presence of an underlying biologically based emotional dysfunction in BPD, including enhanced frontolimbic activation to emotionally aversive cues.

Less is known about neural responding to emotional cues in OD individuals. In OD, heightened activity in response to drug-related cues has been observed in the same frontolimbic regions associated with emotional processing, including amygdala, medial prefrontal cortex, and orbitofrontal cortex (e.g., Yang et al., 2009). In a recent study of reactivity to affective cues in heroin-dependent and non-heroin-dependent control groups, the heroin-dependent participants showed reduced activation in right amygdala to negative versus neutral images (Z. X. Wang et al., 2010). It has been suggested that in drug dependence, neural circuits typically activated by attention, motivation, and emotion are “hijacked,” increasing the salience of drug cues at the expense of other cues (Daglish et al., 2003).

The goal of the current study was to compare responses to affective stimuli between a comorbid OD/BPD sample and healthy controls using functional MRI (fMRI). The experimental task asked participants to attend to a neutral target image in the context of affective and other distractor images. We hypothesized that group differences would be observed in frontolimbic affective processing regions when viewing emotional versus neutral distractors. However, given that OD is associated with dampened emotional responding, whereas BPD is associated with heightened emotional responding, the direction of that difference (i.e., heightened vs. reduced) is unknown.

## Method

### Participants

Twelve male participants (two left-handed, mean age = 30.8 years) who met full diagnostic criteria for both OD and BPD and 12 healthy control subjects (two left-handed, mean age = 32.8 years) participated in the study. Participants in the OD/BPD group were recruited from an outpatient treatment study comparing dialectical behavior therapy and standard individual/group drug counseling as treatments for OD in individuals with BPD. Participants

from both treatment conditions were included. All participants were recruited and scanned at the University of Washington. Control participants were recruited via local and university website and flier advertisements. The inclusion criteria for the OD/BPD treatment study were (a) diagnosis of primary OD, as assessed by the Structured Clinical Interview for *DSM-IV*—Axis I (SCID-I; First et al., 1995); (b) diagnosis of BPD, as assessed by the Structured Clinical Interview for *DSM-IV* Disorders—Axis II (SCID-II; First et al., 1997); (c) no diagnosis of bipolar disorder or psychotic disorders, as assessed by the SCID-I; (d) estimated verbal IQ of 75 or greater, as assessed by the Peabody Picture Vocabulary Test (Dunn & Dunn, 1997); and (e) no current use of prescribed psychiatric medications (e.g., antidepressants). Axis I conditions not specifically ruled out as stated above were permitted (e.g., major depressive disorder, eating disorders, anxiety disorders were allowed). OD/BPD participants had been in treatment for an average of 14.8 weeks, and all OD/BPD participants were taking the opiate replacement medication buprenorphine/naloxone (Suboxone). No other psychoactive medications (e.g., antidepressants) were prescribed or permitted in the protocol, and all previously prescribed psychoactive medications were discontinued or tapered before participants entered the treatment study. Control subjects were lifetime-free of substance abuse or dependence and opiate use, as assessed by the SCID-I, and did not meet criteria for BPD, as assessed by the SCID-II. Further inclusion criteria for all participants included no conditions that would interfere with the safety or quality of MRI scanning (e.g., implanted metal, history of neurological injury, claustrophobia) and male gender. The study was restricted to a single gender in order to reduce gender-related variance in emotion reactivity (Cahill, 2003), and male gender was selected because males are underrepresented in studies of BPD.

Detailed demographic and clinical assessments for the two groups are listed in Table 1. Groups did not differ in age or race/ethnicity, but the control group had a higher average education level than the OD/BPD group. The study was approved for ethical treatment of human subjects by the Institutional Review Boards at the University of Washington and Duke University Medical Center (where pilot

Table 1  
*Demographic and Questionnaire Information for Control and OD/BPD Participants*

Variable	Control ( <i>n</i> = 12)	OD/BPD ( <i>n</i> = 12)
<i>M</i> ( <i>SD</i> ) age (years)	32.8 (13.9) <sub>a</sub>	30.8 (9.5) <sub>a</sub>
<i>M</i> ( <i>SD</i> ) education group	7.5 (1.8) <sub>a</sub>	4.5 (1.5) <sub>b</sub>
Education group: Mode	Some college (6/12)	Some college (5/12)
Racial/ethnic background (%)		
White/Caucasian	50.0 <sub>a</sub>	66.7 <sub>a</sub>
White/Latino	8.3	8.3
Asian	41.56	0.0
Native American	0.0	8.3
Left-handed ( <i>n</i> )	2 <sub>a</sub>	2 <sub>a</sub>
<i>M</i> ( <i>SD</i> ) dissociation score	0.25 (0.58) <sub>a</sub>	1.91 (1.73) <sub>b</sub>

*Note.* OD/BPD = opiate-dependent/borderline personality disorder group. Education groups range from 2 = *some high school* to 10 = *doctoral degree*. Differing subscripts across rows indicate a significant difference at  $p < .05$ ; identical subscripts indicate no statistical difference.

testing and data analyses were conducted), and all subjects provided written informed consent after the procedures had been fully explained.

### Scan Day

Urinalysis (UA) was performed at the beginning of the scan session for both OD/BPD and control groups. UA measured detectable levels of opiates, amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, PCP, marijuana, methadone, and tricyclics (Triage TOX system, Biosite Inc., San Diego, CA). OD/BPD participants received their prescribed dose of buprenorphine/naloxone immediately before the scan. Dissociative symptoms were measured by the four-item Dissociative Symptoms Scale (DSS; Stiglmayr, Shapiro, Stieglitz, Limberger, & Bohus, 2001) before and after the scan. Anatomical and functional images were collected in the same scan session.

### Experimental Design

An “emotional oddball” task (L. Wang et al., 2008; L. Wang, McCarthy, Song, & LaBar, 2005) was administered in which participants were asked to watch for a target image in the context of standard scrambled images as well as negative, neutral, and drug image distractors. All of the distractors were trial-unique. The presentation frequency for targets and negative, drug, and neutral distractors was 2.85% each, with standards making up the remaining 88.6%

of stimuli presented. Participants pressed a response button using their right index finger on detection of a target oddball stimulus (circle) and their right middle finger to all other stimuli. The imaging session consisted of 10 runs, each containing 175 stimuli (stimulus duration = 1,500 ms, interstimulus interval = 2,000 ms). The interval between successive rare stimuli (targets and distractors) was randomized between 16 and 20 s to allow hemodynamic responses to return to baseline.

The present study focused on negative image distractor trials; activation tables for target and drug cue trials are reported in supplemental materials available online.

### Stimuli

The stimuli and design of the emotional oddball task were similar to those described previously (L. Wang et al., 2005). Briefly, distractor images were chosen from the International Affective Picture Set (Lang, Bradley, & Cuthbert, 2005) and images used in previous studies (L. Wang et al., 2005). Negative images included pictures of injury, conflict, and facial displays of negative emotions, and neutral images included everyday scenes of work and shopping as well as neutral facial displays. Drug pictures included scenes of drug use, drug paraphernalia and supplies, social contexts, and money. Distractor images were categorized as negative, neutral, and drug-related based on pilot testing by 11 control and seven OD/BPD participants

(who did not participate in the main study). On a 9-point visual analog scale, negative images averaged valence scores of 2.3 and arousal scores of 6.1; neutral images averaged valence scores of 4.7 and arousal scores of 3.1. The attentional targets were circles of varying sizes and luminance, and the standard stimuli were phase-scrambled and luminance-matched versions of the distractors. All images were converted to grayscale.

### Image Acquisition and Analysis

Magnetic resonance images were acquired on a 3.0 Tesla Phillips Achieva scanner and were analyzed as described previously (L. Wang et al., 2005). High-resolution T1 images were collected using a 3D MPRAGE pulse sequence (a Turbo Field Echo sequence with an inversion pulse) and an R/L SENSE factor of 1.5. Parameters for anatomical scanning were modified over the course of the study; however, all data were normalized to standard space following coregistration, so the impact of these changes should be minimal.<sup>1</sup> Functional 2D radiant echo EPI images were acquired transaxially with the following parameters: TR = 2,000 ms, TE = 30 ms, FOV = 24 × 24 cm, flip angle = 76°, matrix = 64 × 64, 32 contiguous images, slice thickness = 3.8 mm, resulting in 3.75 × 3.75 × 3.8 mm voxels.

Image preprocessing was conducted using temporal realignment for interleaved slice acquisition and spatial realignment to adjust for motion using affine transformation routines implemented in SPM (Wellcome Department of Cognitive Neurology, London, England). The realigned images were coregistered to the anatomical images obtained for each participant and normalized to SPM's template image, which conforms to the Montreal Neurologic Institute's standardized brain space. The voxel size was 3.5 × 3.5 × 3.5 mm<sup>3</sup> after normalization. The functional data were spatially smoothed with an 8-mm isotropic Gaussian kernel prior to statistical analysis.

The voxel-wise and region of interest (ROI) analyses used custom MATLAB scripts (Pelphrey et al., 2003; Dolcos & McCarthy, 2006; L. Wang, LaBar, & McCarthy, 2006). Event epochs were extracted for a voxel-based event-related analysis and a functional ROI analysis. The hemodynamic response was time-locked to the onset of each image of interest (negative and

neutral distractors). The whole epoch of each event was extracted from -4 s before the onset of the stimulus to 14 s postonset. Voxel-based signal percentage change at each postonset time point (from 0 s to +14 s) was calculated for each subject by subtracting the mean prestimulus baseline activity (activity to scrambled pictures presented from -4 s to 0 s prior to each event) and then averaging across all trials with the same event type. We validated the hemodynamic time course at each voxel by testing the correlation of the hemodynamic response across time with the canonical gamma hemodynamic response for each event in each subject.

Statistical contrasts at each time point were set up using a random-effect analysis to calculate signal differences between the conditions of interest across each group of participants. Statistical *t* maps at each time point were derived for the events of interest, resulting in a *t* statistic for every voxel. This sequential approach accounts for intersubject variability and permits generalization to the population at large. Only the results at peak time point 6 s poststimulus are reported here. Only those voxels whose hemodynamic responses were significantly correlated with the canonical hemodynamic response (false discovery rate-corrected  $p < .01$  with a spatial extent of five contiguous voxels) were entered into further within- and between-groups analyses. Two-sample *t* tests were conducted to compare voxel-wise signal changes at the peak time point (6 s poststimulus) between OD/BPD and controls for each negative image, thresholded at  $p < .001$ , uncorrected with a spatial extent of five contiguous voxels. Regions were identified using Harvard-Oxford and Talairach atlases.

To visualize the hemodynamic response profile for each functional region, we performed an ROI analysis. The middle frontal gyrus (MFG), anterior cingulate gyrus (ACG), amygdala, and

<sup>1</sup> For the first four subjects, images were collected in the sagittal plane with the following parameters: repetition time (TR) = 7.0 ms, echo time (TE) = 3.25 ms, 160 contiguous images, slice thickness = 1 mm. The last 20 subjects were scanned with the following T1 parameters: TR = 7.6 ms, TE = 3.7 ms, 64 contiguous images, slice thickness = 1.9 mm. Ten subjects were collected in the axial plane, and the remaining subjects were collected in oblique axial orientation, parallel to the AC-PC line. For all subjects, field of view (FOV) = 24 × 24 cm, flip angle = 8°, reconstruction matrix = 256 × 256.

hippocampus were chosen as ROIs on the basis of previous study results (L. Wang et al., 2005, 2006, 2008). The mean signal change within each ROI was computed for each time point for each event. Only regions demonstrating voxel-based cluster group differences in  $t$  values at  $p < .01$  in the present study were further analyzed. To confirm the voxel-based findings, we conducted a statistical analysis using analysis of variance (ANOVA) on the ROIs, focused on the mean percentage signal change by hemisphere at the peak time point (6 s poststimulus). A 2 (type: negative, neutral)  $\times$  2 (group: OD/BPD, control) ANOVA was performed.

## Results

### Sample Characteristics

UA results were negative for opiates for eight of 12 OD/BPD participants. The most common positive nonopiate result was for THC (9/12 positive), followed by cocaine (2/12), benzodiazepines (1/12), and amphetamine (1/12). Among controls, one participant was positive for THC, and the remaining 11 were negative for all substances.

### Reaction Time and Self-Report

We conducted  $t$  tests to compare square-root transformed in-scanner reaction times (RTs) between groups. The OD/BPD and control groups did not differ in their RTs to negative,  $t(22) = 0.31$ ,  $p = .75$ , or neutral stimuli,  $t(22) = 0.76$ ,  $p = .45$ . In rating the valence and arousal levels elicited by each image after the scan, data for two control participants and three OD/BPD participants were discarded because of systematically repeated ratings (used the same number for all ratings) and notably short ( $<300$  ms) RTs. Subjective valence and arousal ratings for negative and neutral distractors were analyzed using 2 (distractor valence: negative, neutral)  $\times$  2 (group: OD/BPD, control) multivariate analyses of variance for valence and arousal ratings. For valence ratings, there was a significant main effect of distractor valence,  $F(1, 17) = 38.83$ ,  $p < .00001$ , such that negative images were rated more negative than neutral images. The main effect of group was not significant,  $F(1, 17) = 0.91$ ,  $p = .34$ , nor was the Distractor Valence  $\times$  Group interaction,  $F(1, 17) = 0.79$ ,

$p = .44$ . Similarly for arousal ratings, there was a significant main effect of distractor valence,  $F(1, 17) = 29.72$ ,  $p = .00004$ , such that negative images were rated more arousing than neutral images. The main effect of group was not significant,  $F(1, 17) = 0.04$ ,  $p = .84$ , nor was the Distractor Valence  $\times$  Group interaction,  $F(1, 17) = 0.03$ ,  $p = .86$ . Average image ratings and RTs are included in Supplemental Table 3. Finally, pre- and postscan dissociative symptom scores were averaged, and  $t$  tests were used to compare scores between groups. Consistent with dissociation as a symptom of BPD, dissociation scores were higher in the OD/BPD group than in controls,  $t(22) = 3.16$ ,  $p = .005$ . Scores are reported in Table 1.

### fMRI

A direct statistical comparison between the OD/BPD and control groups revealed activity reductions in the OD/BPD group to negative images (negative–neutral distractor contrast) in emotional processing regions including bilateral amygdala, extending to hippocampus; ACG; and left subgenual cingulate. The OD/BPD group showed greater activation than controls to negative images in left inferior frontal gyrus (see Table 2 and Figure 1). Follow-up 2 (group: OD/BPD, control)  $\times$  2 (distractor: negative, neutral) ANOVAs were performed for the fronto-cingulate-limbic ROIs;  $p$  values were Bonferroni-corrected to a significance value of  $p < .007$ . Group  $\times$  Distractor interactions were observed in dorsal ACG, left and right amygdala (basal frontal and extended amygdala), right MFG, and left hippocampus, whereby controls, but not OD/BPD participants, showed greater activation to negative than neutral stimuli.<sup>2</sup>

### Effects of Recent Substance Use and Dissociation

To address the potential effects of recent substance use on activation in fronto-cingulate-limbic ROIs, we coded the number of substances with positive UAs at the fMRI scan for

<sup>2</sup> When education level was used as a covariate in ROI analyses, there were no significant effects of, or interactions with, the education variable. The overall pattern of results was consistent when education level was used as a covariate.

Table 2  
*Brain Regions Associated With Activation to Negative Versus Neutral Targets (Threshold  $p < .001$ )*

Group	Region	BA	Hemisphere	Maximum $t$	MNI coordinates			Cluster size
					$x$	$y$	$z$	
Control > OD/BPD	Subgenual cingulate	25	L	3.93	-4	14	11	6
	Superior frontal gyrus	6	R	4.05	16	12	62	6
	Anterior cingulate gyrus	24	Midline	5.02	0	4	35	8
	Amygdala	—	R	5.01	25	4	-18	19
		—	L	4.71	-25	4	-18	14
	Precentral gyrus	6	R	5.27	44	-2	50	23
	Precentral gyrus	6	R	4.51	42	-7	49	7
	Thalamus	—	R	4.03	7	-18	7	6
	Cerebellum	—	R	4.10	14	-46	-11	9
	Superior parietal sulcus	7	L	4.86	-35	-60	60	19
OD/BPD > Control	Inferior frontal gyrus	45	L	4.87	-53	39	7	12

Note. BA = Brodmann Area; OD/BPD = opiate-dependent/borderline personality disorder group; MNI = Montreal Neurologic Institute; R = right; L = left.

all participants (range: 0–4). Follow-up 2 (group: OD/BPD, control)  $\times$  2 (distractor: negative, neutral) ANOVAs for ROIs were repeated, adding the positive UA variable as a covariate. There were no significant effects of, or interactions with, the positive UA variable. The overall pattern of results was consistent when positive UAs were used as a covariate, using a conventional  $p < .05$  criteria for significance. Similarly, the presence or absence of a positive screen for opiates was added as a covariate in a separate set of analyses. Again, there were no significant effects of, or interactions with, the positive opiate variable.

DSS scores were used as a covariate in an additional series of Group  $\times$  Distractor ANOVAs predicting ROI activation levels. Again, the overall pattern of results was unchanged when including DSS scores as a covariate, using a conventional  $p < .05$  criteria for significance. For dorsal ACG, left and right amygdala, and right MFG, there was no significant main effect of DSS score or interaction between DSS scores and image valence. For left hippocampus, a significant main effect of dissociation was observed,  $F(1, 21) = 14.23$ ,  $p = .001$ , as was an interaction between image valence and DSS scores,  $F(1, 21) = 5.22$ ,  $p = .03$ . There was a significant negative correlation between DSS scores and hippocampal activation to both negative and neutral distractors,  $r = .54$ ,  $p = .007$ , and  $r = .58$ ,  $p = .003$ , respectively.

## Discussion

The goal of the present study was to compare affective processing between OD/BPD and control groups. The OD/BPD group showed reduced neural reactivity to negative distractors in regions associated with affective processing (amygdala, ACG) when compared with controls. These results are inconsistent with previous studies of emotion reactivity in BPD, which have generally found relatively heightened amygdala activation (Donegan et al., 2003; Driessen et al., 2004; Herpertz et al., 2001; Koenigsberg et al., 2009; Minzenberg et al., 2007). However, these results are consistent with findings of reduced recognition of, and physiological reactivity to, negative cues in OD (Gerra et al., 2003; Kornreich et al., 2003; Z. X. Wang et al., 2010). In the presence of comorbid OD/BPD, it appears that neural activity to emotional cues follows patterns more consistent with substance use than with personality disorder processes.

One potential explanation for reduced ACG and amygdala activation in the OD/BPD group is that opiate use in BPD is driven, in part, by an attempt to reduce hyperresponsivity to negative affective cues (cf. Trull et al., 2000), which may in fact be successful. Also, buprenorphine administration, a component of the buprenorphine/naloxone maintenance medication used by study participants, is thought to reduce negative affect via its effect on opiate receptors

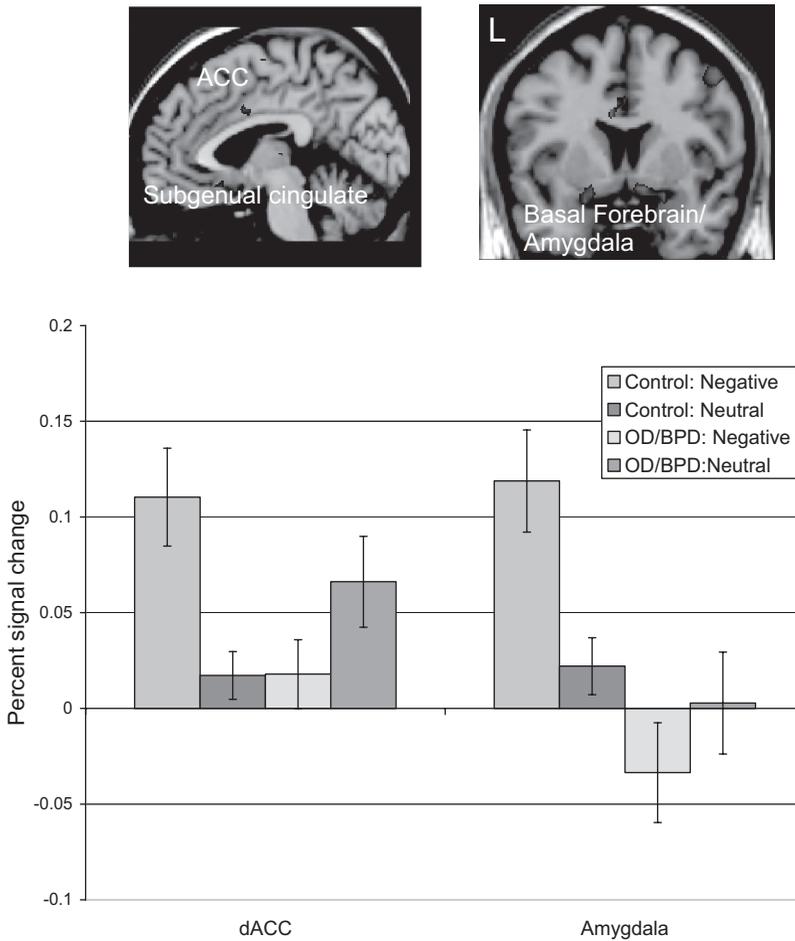


Figure 1. Voxel-based random effect analysis for negative targets at the peak time point. Significantly decreased activation in the opiate-dependent/borderline personality disorder (OD/BPD) group compared with the control group from a two-sample  $t$  test on activation to the negative minus neutral contrast at the peak time point ( $p < .001$ , uncorrected, spatial extent of five contiguous voxels). The mean percentage signal change in dorsal ACC (dACC) and amygdala (averaged over left and right hemispheres) at the peak time point is shown in the graphs below each image. Error bars reflect standard error of the mean. ACC = anterior cingulate cortex; L = left hemisphere; R = right hemisphere.

(Gerra et al., 2006), although buprenorphine/naloxone-maintained OD subjects still rated negative affect higher than controls following a chemical stressor (Kakko et al., 2008). It should be noted that in the present study, participant groups did not differ in their reported emotional responses to negative images. Effects of buprenorphine on neural activity are mixed, with a PET study showing broad reductions in cortical glucose metabolism following buprenorphine injection (Walsh et al., 1994) and an fMRI study

showing increases in dorsal ACC activation in methadone- or buprenorphine/naloxone-maintained OD subjects during a cognitive task (Yucel et al., 2007). Acute buprenorphine administration has been observed to potentiate striatal activation and attenuate somatosensory cortex and thalamic activation in the context of a pain stressor, but effects on ACC and amygdala are not reported (Upadhyay et al., 2009). Thus, it is unclear what specific effect buprenorphine/naloxone had on study results.

The degree of dissociative symptoms, although higher in the OD/BPD group, did not account for reduced ACC and amygdala activations. Whether as a result of short-term administration of maintenance medication, long-term opiate use, or other factors, individuals with comorbid OD/BPD do not show the expected amygdalar, cingulate, or medial prefrontal hyperactivation to negative cues characteristic of BPD.

This is the first fMRI study of which we are aware that has examined comorbid OD/BPD, a severe condition with poor treatment outcomes. The use of male subjects provides a unique contribution to the BPD literature, which often focuses exclusively on female participants (e.g., Driessen et al., 2000, 2004; Herpertz et al., 2001; Schnell & Herpertz, 2007; only one male BPD participant in Silbersweig et al., 2007). However, it is uncertain whether gender differences contributed to the finding of reduced emotion network activation in the OD/BPD sample, and further replication in a mixed-gender sample is in order.

There were additional limitations to the study, which restrict its interpretability and require further replication and expansion. Recent substance use by the OD/BPD group may have caused differences in stimulus perception or regional blood flow that are more related to state effects than trait or diagnosis-specific effects. Continued substance use is a problem in OD research using populations not in restricted treatment environments; it is frequently observed in OD individuals engaged in outpatient treatment (Gruber, Delucchi, Kielstein, & Batki, 2008; Linehan et al., 2002) and has been observed in previous neuroimaging studies of OD individuals in outpatient treatment (e.g., Ersche et al., 2006). However, as reported above, entering the number of UA-positive substances or presence of recent opiate use as a covariate in ROI analyses did not reveal any significant main effects or interactions, suggesting that the impact of acute substance use was not pronounced. Future studies comparing individuals using opiate replacement medications with those not using medications are required to determine their impact. As in much of the clinical fMRI literature, the sample size is modest. Future larger scale studies also would do well to include BPD-only and OD-only comparison groups to help tease apart the

relative contribution of the two disorders, versus any synergistic effects of comorbidity within individuals.

In conclusion, this study, despite its preliminary nature, is an important first step in characterizing the neurological basis of emotional processing in comorbid personality and substance dependence disorders, and in this clinically challenging population in particular. Reduced activation was seen to emotional stimuli, hewing more closely to effects seen in OD than in BPD, a finding that may help inform interventions focused on emotion regulation in this population. It is critical to expand the study of the neurological underpinnings of disorders beyond single-diagnosis samples if we are to fully understand the nature of disordered real-world populations.

## References

- Brooner, R. K., King, V. L., Kidorf, M., Schmidt, C. W., Jr., & Bigelow, G. E. (1997). Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Archives of General Psychiatry*, *54*, 71–80.
- Cahill, L. (2003). Sex-related influences on the neurobiology of emotionally influenced memory. *Annals of the New York Academy of Sciences*, *985*, 163–173.
- Daglish, M. R., Weinstein, A., Malizia, A. L., Wilson, S., Melichar, J. K., Lingford-Hughes, A., . . . Nutt, D. J. (2003). Functional connectivity analysis of the neural circuits of opiate craving: “More” rather than “different”? *NeuroImage*, *20*, 1964–1970.
- Darke, S., Ross, J., Williamson, A., Mills, K. L., Havard, A., & Teesson, M. (2007). Borderline personality disorder and persistently elevated levels of risk in 36-month outcomes for the treatment of heroin dependence. *Addiction*, *102*, 1140–1146.
- Dolcos, F., & McCarthy, G. (2006). Brain systems mediating cognitive interference by emotional distraction. *Journal of Neuroscience*, *26*, 2072–2079.
- Domes, G., Czeschnek, D., Weidler, F., Berger, C., Fast, K., & Herpertz, S. C. (2008). Recognition of facial affect in borderline personality disorder. *Journal of Personality Disorders*, *22*, 135–147.
- Donegan, N. H., Sanislow, C. A., Blumberg, H. P., Fulbright, R. K., Lacadie, C., Skudlarski, P., . . . Wexler, B. E. (2003). Amygdala hyperactivity in borderline personality disorder: Implications for emotional dysregulation. *Biological Psychiatry*, *54*, 1284–1293.

- Driessen, M., Beblo, T., Mertens, M., Piefke, M., Rullkoetter, N., Silva-Saavedra, A., . . . Woermann, F. G. (2004). Posttraumatic stress disorder and fMRI activation patterns of traumatic memory in patients with borderline personality disorder. *Biological Psychiatry, 55*, 603–611.
- Driessen, M., Herrmann, J., Stahl, K., Zwaan, M., Meier, S., Hill, A., . . . 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.
- Dunn, L. M., & Dunn, L. M. (1997). Examiner's manual for the PPVT-III. Circle Pines, MN: American Guidance Service.
- Ebner-Priemer, U. W., Badeck, S., Beckmann, C., Wagner, A., Feige, B., Weiss, I., . . . Bohus, M. (2005). Affective dysregulation and dissociative experience in female patients with borderline personality disorder: A startle response study. *Journal of Psychiatric Research, 39*, 85–92.
- Ebner-Priemer, U. W., Welch, S. S., Grossman, P., Reisch, T., Linehan, M. M., & Bohus, M. (2007). Psychophysiological ambulatory assessment of affective dysregulation in borderline personality disorder. *Psychiatry Research, 150*, 265–275.
- Ersche, K. D., Fletcher, P. C., Roiser, J. P., Fryer, T. D., London, M., Robbins, T. W., & Sahakian, B. J. (2006). Differences in orbitofrontal activation during decision-making between methadone-maintained opiate users, heroin users and healthy volunteers. *Psychopharmacology (Berl), 188*, 364–373.
- First, M. B., Gibbon, M., Spitzer, R. L., Williams, J. B. W., & Benjamin, L. S. (1997). Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II). Washington, D.C.: American Psychiatric Press, Inc.
- First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1995). Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P, Version 2.0): Biometrics Research Department, New York State Psychiatric Institute.
- Gerra, G., Baldaro, B., Zaimovic, A., Moi, G., Bussandri, M., Raggi, M. A., & Brambilla, F. (2003). Neuroendocrine responses to experimentally-induced emotions among abstinent opioid-dependent subjects. *Drug & Alcohol Dependence, 71*, 25–35.
- Gerra, G., Leonardi, C., D'Amore, A., Strepparola, G., Fagetti, R., Assi, C., . . . Lucchini, A. (2006). Buprenorphine treatment outcome in dually diagnosed heroin dependent patients: A retrospective study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 30*, 265–272.
- Grant, B. F., Chou, S. P., Goldstein, R. B., Huang, B., Stinson, F. S., Saha, T. D., . . . Ruan, W. J. (2008). Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: Results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry, 69*, 533–545.
- Gruber, V. A., Delucchi, K. L., Kielstein, A., & Batki, S. L. (2008). A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug & Alcohol Dependence, 94*, 199–206.
- Herpertz, S. C., Dietrich, T. M., Wenning, B., Krings, T., Erberich, S. G., Willmes, K., . . . Sass, H. (2001). Evidence of abnormal amygdala functioning in borderline personality disorder: A functional MRI study. *Biological Psychiatry, 50*, 292–298.
- Herpertz, S. C., Kunert, H. J., Schwenger, U. B., & Sass, H. (1999). Affective responsiveness in borderline personality disorder: A psychophysiological approach. *The American Journal of Psychiatry, 156*, 1550–1556.
- Herpertz, S. C., Schwenger, U. B., Kunert, H. J., Lukas, G., Gretzer, U., Nutzmann, J., . . . Sass, H. (2000). Emotional responses in patients with borderline as compared with avoidant personality disorder. *Journal of Personality Disorders, 14*, 339–351.
- Kakko, J., von Wachenfeldt, J., Svanborg, K. D., Lidstrom, J., Barr, C. S., & Heilig, M. (2008). Mood and neuroendocrine response to a chemical stressor, metyrapone, in buprenorphine-maintained heroin dependence. *Biological Psychiatry, 63*, 172–177.
- Koenigsberg, H. W., Harvey, P. D., Mitropoulou, V., Schmeidler, J., New, A. S., Goodman, M., & Siever, L. J. (2002). Characterizing affective instability in borderline personality disorder. *The American Journal of Psychiatry, 159*, 784–788.
- Koenigsberg, H. W., Siever, L. J., Lee, H., Pizzarello, S., New, A. S., Goodman, M., . . . Prohovnik, I. (2009). Neural correlates of emotion processing in borderline personality disorder. *Psychiatry Research: Neuroimaging, 172*, 192–199.
- Kornreich, C., Foisy, M. L., Philippot, P., Dan, B., Tecco, J., Noel, X., . . . Verbanck, P. (2003). Impaired emotional facial expression recognition in alcoholics, opiate dependence subjects, methadone maintained subjects and mixed alcohol-opiate antecedents subjects compared with normal controls. *Psychiatry Research, 119*, 251–260.
- Kosten, T. A., Kosten, T. R., & Rounsaville, B. J. (1989). Personality disorders in opiate addicts show prognostic specificity. *Journal of Substance Abuse Treatment, 6*, 163–168.
- Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2005). International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-6. Gainesville, FL: University of Florida.
- Linehan, M. M., Dimeff, L. A., Reynolds, S. K., Comtois, K. A., Welch, S. S., Heagerty, P., &

- Kivlahan, D. R. (2002). Dialectical behavior therapy versus comprehensive validation therapy plus 12-step for the treatment of opioid dependent women meeting criteria for borderline personality disorder. *Drug & Alcohol Dependence*, *67*, 13–26.
- Liu, N., Li, B., Sun, N., & Ma, Y. (2008). Effects of addiction-associated and affective stimuli on the attentional blink in a sample of abstinent opiate dependent patients. *Journal of Psychopharmacology*, *22*, 64–70.
- Lubman, D. I., Yucel, M., Kettle, J. W., Scaffidi, A., Mackenzie, T., Simmons, J. G., & Allen, N. B. (2009). Responsiveness to drug cues and natural rewards in opiate addiction: Associations with later heroin use. *Archives of General Psychiatry*, *66*, 205–212.
- Lynch, T. R., Rosenthal, M. Z., Kosson, D. S., Cheavens, J. S., Lejuez, C. W., & Blair, R. J. (2006). Heightened sensitivity to facial expressions of emotion in borderline personality disorder. *Emotion*, *6*, 647–655.
- Marques-Teixeira, J. E., & Santos Barbosa, M. F. (2005). Emotional states and informational brain processing in drug addicts free of drugs: An ERPs study. *International Journal of Psychiatry in Clinical Practice*, *9*, 213–220.
- Minzenberg, M. J., Fan, J., New, A. S., Tang, C. Y., & Siever, L. J. (2007). Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: An event-related fMRI study. *Psychiatry Research*, *155*, 231–243.
- New, A. S., Hazlett, E. A., Buchsbaum, M. S., Goodman, M., Mitelman, S. A., Newmark, R., . . . Siever, L. J. (2007). Amygdala-prefrontal disconnection in borderline personality disorder. *Neuropsychopharmacology*, *32*, 1629–1640.
- Pelphrey, K. A., Mitchell, T. V., McKeown, M. J., Goldstein, J., Allison, T., & McCarthy, G. (2003). Brain activity evoked by the perception of human walking: controlling for meaningful coherent motion. *Journal of Neuroscience*, *23*, 6819–6825.
- Rosenthal, M. Z., Gratz, K. L., Kosson, D. S., Cheavens, J. S., Lejuez, C. W., & Lynch, T. R. (2008). Borderline personality disorder and emotional responding: A review of the research literature. *Clinical Psychology Review*, *28*, 75–91.
- Sansone, R. A., Whitecar, P., & Wiederman, M. W. (2008). The prevalence of borderline personality among buprenorphine patients. *International Journal of Psychiatry in Medicine*, *38*, 217–226.
- Schnell, K., & Herpertz, S. C. (2007). Effects of dialectic-behavioral-therapy on the neural correlates of affective hyperarousal in borderline personality disorder. *Journal of Psychiatric Research*, *41*, 837–847.
- Silbersweig, D., Clarkin, J. F., Goldstein, M., Kernberg, O. F., Tuescher, O., Levy, K. N., . . . Stern, E. (2007). Failure of frontolimbic inhibitory function in the context of negative emotion in borderline personality disorder. *The American Journal of Psychiatry*, *164*, 1832–1841.
- Skodol, A. E., Gunderson, J. G., Pfohl, B., Widiger, T. A., Livesley, W. J., & Siever, L. J. (2002). The borderline diagnosis: I. Psychopathology, comorbidity, and personality structure. *Biological Psychiatry*, *51*, 936–950.
- Stein, K. F. (1996). Affect instability in adults with a borderline personality disorder. *Archives of Psychiatric Nursing*, *10*, 32–40.
- Stiglmayr, C. E., Shapiro, D. A., Stieglitz, R. D., Limberger, M. F., & Bohus, M. (2001). Experience of aversive tension and dissociation in female patients with borderline personality disorder—A controlled study. *Journal of Psychiatric Research*, *35*, 111–118.
- Trull, T. J., Sher, K. J., Minks-Brown, C., Durbin, J., & Burr, R. (2000). Borderline personality disorder and substance use disorders: A review and integration. *Clinical Psychology Review*, *20*, 235–253.
- Trull, T. J., Solhan, M. B., Tragesser, S. L., Jahng, S., Wood, P. K., Piasecki, T. M., & Watson, D. (2008). Affective instability: Measuring a core feature of borderline personality disorder with ecological momentary assessment. *Journal of Abnormal Psychology*, *117*, 647–661.
- Upadhyay, J., Anderson, J., Schwarz, A. J., Baumgartner, R., Coimbra, A., George, E., Knudsen, J., Bishop, J., Natile, L., Robertson, B., Schreiber, R., Iyengar, S., Bleakman, D., Hargreaves, R., Becerra, L., & Borsook, D. (2009). fMRI measures of drug modulation of CNS activation by noxious stimuli: Differential effects of a failed analgesic (fosaprepitant) vs. an opioid analgesic (buprenorphine). *NeuroImage*, *47*(Supp. 1), S62.
- Verdejo-Garcia, A., Perez-Garcia, M., & Bechara, A. (2006). Emotion, decision-making and substance dependence: A somatic-marker model of addiction. *Current Neuropharmacology*, *4*, 17–31.
- Verdejo-Garcia, A., Rivas-Perez, C., Vilar-Lopez, R., & Perez-Garcia, M. (2007). Strategic self-regulation, decision-making and emotion processing in poly-substance abusers in their first year of abstinence. *Drug & Alcohol Dependence*, *86*, 139–146.
- Wagner, A. W., & Linehan, M. M. (1999). Facial expression recognition ability among women with borderline personality disorder: Implications for emotion regulation? *Journal of Personality Disorders*, *13*, 329–344.
- Walsh, S. L., Gilson, S. F., Jasinski, D. R., Stapleton, J. M., Phillips, R. L., Dannals, R. F., Schmidt, J., Preston, K. L., Grayson, R., Bigelow, G. E., Sullivan, J. T., Contoreggi, C., & London, E. D. (1994). Buprenorphine reduces cerebral glucose

- metabolism in polydrug abusers. *Neuropsychopharmacology*, *10*, 157–170.
- Wang, L., LaBar, K. S., & McCarthy, G. (2006). Mood alters amygdala activation to sad distractors during an attentional task. *Biological Psychiatry*, *60*, 1139–1146.
- Wang, L., LaBar, K. S., Smoski, M. J., Rosenthal, M. Z., Dolcos, F., Lynch, T. R., . . . McCarthy, G. (2008). Prefrontal mechanisms for executive control over emotional distraction are altered in major depression. *Psychiatry Research*, *163*, 143–155.
- Wang, L., McCarthy, G., Song, A. W., & LaBar, K. S. (2005). Amygdala activation to sad pictures during high-field (4 tesla) functional magnetic resonance imaging. *Emotion*, *5*, 12–22.
- Wang, Z. X., Zhang, J. X., Wu, Q. L., Liu, N., Hu, X. P., Chan, R. C., & Xiao, Z. W. (2010). Alterations in the processing of non-drug-related affective stimuli in abstinent heroin addicts. *NeuroImage*, *49*, 971–976.
- Yang, Z., Xie, J., Shao, Y. C., Xie, C. M., Fu, L. P., Li, D. J., . . . Li, S. J. (2009). Dynamic neural responses to cue-reactivity paradigms in heroin-dependent users: An fMRI study. *Human Brain Mapping*, *30*, 766–775.
- Yucel, M., Lubman, D. I., Harrison, B. J., Fornito, A., Allen, N. B., Wellard, R. M., . . . Pantelis, C. (2007). A combined spectroscopic and functional MRI investigation of the dorsal anterior cingulate region in opiate addiction. *Molecular Psychiatry*, *12*, 611, 691–702.

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