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## Hyper-modulation of brain networks by the amygdala among women with Borderline Personality Disorder: Network signatures of affective interference during cognitive processing

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### Abstract

Emotion dysregulation is a core characteristic of patients with Borderline Personality Disorder (BPD), and is often attributed to an imbalance in fronto-limbic network function. Hyperarousal of amygdala, especially in response to negative affective stimuli, results in affective interference with cognitive processing of executive functions. Clinical consequences include the impulsive-aggression, suicidal and self-injurious behaviors which characterize BPD. Dysfunctional interactions between amygdala and its network targets have not been well characterized during cognitive task performance. Using psychophysiological interaction analysis (PPI), we mapped network profiles of amygdala interaction with key regulatory regions during a Go No-Go task, modified to use negative, positive and neutral Ekman faces as targets. Fifty-six female subjects, 31 BPD and 25 healthy controls (HC), completed the affectively valenced Go No-Go task during fMRI scanning. In the negative affective condition, the amygdala exerted greater modulation of its targets in BPD compared to HC subjects in Rt. OFC, Rt. dACC, Rt. Parietal cortex, Rt. Basal Ganglia, and Rt. dlPFC. Across the spectrum of affective contrasts, hypermodulation in BPD subjects observed the following ordering: Negative > Neutral > Positive contrast. The amygdala seed exerted modulatory effects on specific target regions important in processing response inhibition and motor impulsiveness. The vulnerability of BPD subjects to affective interference with impulse control may be due to specific network dysfunction related to amygdala hyperarousal and its effects on prefrontal regulatory regions such as the OFC and dACC.

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#### Contributors.

Paul Soloff was involved in the study design, analysis, interpretation and manuscript writing. Kristy Abraham, Karthik Ramaseshan, and Ashley Burgess were involved in data analysis. Vaibhav A. Diwadkar was involved in the study design, analysis, interpretation, and manuscript writing.

#### Conflicts of Interest:

There are no conflicts of interest with any of the authors.

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## Keywords

Borderline Personality Disorder; fMRI; amygdala; psychophysiological interactions; cognition; impulsiveness

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## Introduction

Emotion dysregulation is a core diagnostic characteristic of Borderline Personality Disorder (BPD), and is considered by some to be the primary source of behavioral pathology in this illness (Linehan, 1993). In laboratory studies, patients with BPD respond more intensely and for longer durations to negative emotional stimuli, and are slower to return to baseline than healthy controls (Jacob et al., 2008, Levine et al., 1997). In studies using electronic monitoring in the natural environment, BPD subjects demonstrate more affective instability, hypersensitivity, extreme changes of mood, negative and conflicting emotions compared to controls (Ebner-Priemer et al., 2007a,b, 2008, Reisch et al., 2008, Trull et al., 2008). Current theories of emotion regulation postulate a balance between “top down” cortical modulation and “bottom up” limbic arousal. i.e. Dysregulation of emotion may result from either hyper-arousal of the limbic system, especially in response to aversive stimuli, or, conversely, diminished efficacy of tonic cortical inhibition (Ochsner & Gross, 2006, Gross & Thompson, 2006, Phillips et al., 2008, Davidson et al., 2000). The affective instability of the borderline patient is attributed to an imbalance in fronto-limbic network function involving the amygdala and associated regions of the limbic system, and regulatory regions in prefrontal cortex (PFC), including the orbital frontal cortex (OFC), anterior cingulate cortex (ACC), dorso-lateral PFC (dlPFC) and associated areas (Schulze et al., 2016). fMRI studies have repeatedly demonstrated increased arousal of the amygdala in BPD compared to control subjects in response to provocations using emotional stimuli such as the affectively valenced Ekman faces (Donegan et al., 2003, Minzenberg et al., 2007), aversive IAPS scenes (Herpertz et al., 2001, Schulze et al., 2010, Hazlett et al., 2012), unresolved life events (Beblo et al., 2006), emotional scripts (Schmahl et al., 2003, Schmahl and Bremner, 2006), and negative social pictures (Koenigsberg et al., 2014). BPD subjects show prolonged BOLD responses in amygdala to emotional stimuli, indicating longer time to return to baseline, and a failure to down-regulate (habituate) amygdala responses with repeated presentations of emotional pictures, suggesting a deficit in regulating emotional arousal (Hazlett et al., 2012). Hyper-arousal of the amygdala is clinically important, given its role in appraising the affective salience of stimuli, especially facial expressions (Calder and Young, 2005), and in the appraisal of perceived threat and mediation of fear responses (LeDoux, 1993). In this investigation we extend previous work in BPD by assessing dysfunctional network profiles of the amygdala in the context of an affective impulsivity paradigm (Soloff et al., 2015).

Anatomical network connectivity, and functional interactions of the amygdala have been systematically studied using both animal and human models (Diwadkar et al., 2012; Phelps and LeDoux, 2005); however, *dysfunctional interactions* between the amygdala and its network targets have not been well-characterized in BPD. Thus, while *hyper*-activation of the amygdala is a characteristic of impaired *functional brain responses* in BPD, the

directional network effects exerted by the amygdala in BPD are relatively under-studied using network analyses of fMRI signals. Understanding these network profiles will contribute greatly toward assessing the contribution of “bottom-up” signals in driving some of the core characteristics of emotional dysregulation and how they might affect cognitive processing in BPD.

While it is clear that the brain’s cognitive systems are not insulated from affective interference, the *network profiles of the amygdala during cognitive processing* have not been well characterized (Phelps, 2006). The OFC, ACC, dlPFC, and associated areas, are involved in executive cognitive functions such as focused attention, response inhibition, conflict resolution, encoding and recall of memory. Through extensive feedback loops to limbic structures, these prefrontal regions exercise a measure of “top-down” tonic control to maintain emotional homeostasis (Davidson and Irwin, 1999). In patients with BPD, affective interference, especially by negative stimuli, impairs functioning of brain networks that subserve cognitive processing of executive functions required for adaptive responding (Sebastian et al., 2013; Soloff et al., 2015; Winter et al., 2014).

We have been studying the effects of affect on brain responses during cognitive processing in BPD using paradigms specifically modified to utilize and permute affective context. In relying on affective appraisal to gate cognitive processing, we seek to force integration of affective and cognitive domains (Blair et al., 2007), and to assess if this integration differentially affects brain responses in BPD.

A particular focus of our work is the borderline patient’s trait impulsivity, a diagnostic characteristic of the disorder which is clinically associated with affective instability, aggression, suicidal and self-destructive behaviors (Brodsky et al., 2006). Impulsive-aggressive behavior in BPD is associated with structural, metabolic, and functional abnormalities in fronto-limbic networks (Berlin et al., 2005, Sebastian et al., 2013, Siever 2008). Impulsive, aggressive, and self-destructive behaviors in BPD occur most often in the context of negative affectivity, especially perceived rejection (Yen et al., 2004). fMRI studies of impulse control which incorporate negative emotional stimuli, demonstrate fronto-limbic dysfunction in BPD compared to control subjects (Jacob et al., 2013, Sebastian et al. 2014). Given the clinical relevance of impulsivity in BPD, we have focused attention on the role of emotional interference with this executive function using an affectively-modified Go-No-Go paradigm.

The classic version of this paradigm requires participants to gate their responses to rapidly presented stimuli based on perceptual identity. In our affective Go No-Go paradigm, positive, negative and neutral Ekman faces are used to mediate impulse control (i.e. response inhibition), depending on the affective (rather than perceptual) gating of the response (Soloff et al., 2015). As a result, it is possible to isolate the selective effects of the affective context of the response on fMRI responses, and particularly, on brain network interactions. Using the affective Go No-Go paradigm under negative affective conditions in subjects with BPD, we previously reported increased activation in amygdala, and increased and decreased activation in different regions of the middle-inferior OFC. Robust increases were also noted in areas reflecting task-relevant processing: the superior parietal/precuneus (for visuo-spatial

processing and episodic visual memory), and the basal ganglia (for reward-based decision-making)(Soloff et al., 2015). The current extension of our work is specifically focused on the network profiles of the amygdala, relying on modeling psycho-physiological interactions (PPI) in the fMRI data (Friston et al., 1997; Horwitz et al., 2005; J. X. O'Reilly, M. W. Woolrich, T. E. Behrens, S. M. Smith, & H. Johansen-Berg, 2012).

The use of PPI was motivated by its analytic value, positioned as it is between techniques of functional and maximal effective connectivity analyses (Stephan et al, 2016, Silverstein et al., 2016), providing a robust model for investigation of seed-based network interactions (Friston, 2011; Friston et al., 1997; Kim & Horwitz, 2008; Woodcock, Wadehra, & Diwadkar, 2016). PPI estimates directional modulation by an *a priori* defined seed region (e.g., amygdala) on target regions (e.g., OFC) in the context of a psychological contrast of interest (e.g., negative > positive affective context) (Friston et al., 1997). The framework for network explorations using fMRI data is vast, with the availability of a rich set of well defined quantitative models. We chose PPI to explore differential interactions between the amygdala and its targets, in BPD relative to controls. PPIs afford rapid and efficient exploration of pairwise directional network effects between seed regions and targets (Silverstein et al., 2016) and are particularly useful when the choice of seed is well motivated (in our case, the amygdala). This model is more simplistic than more complex dynamic causal models of network interactions (or “effective connectivity” analyses) yet is a useful “first step” in divining dysfunctional network profiles in disorders ranging from schizophrenia (Wadehra et al., 2013) to obsessive compulsive disorder (Diwadkar et al., 2015; Friedman et al., In Press). In this analysis, we use PPI in elucidating “bottom-up” profiles of the amygdala during response inhibition in BPD, as well as *mechanisms* of affective interference at the level of brain network interactions.

## Method

The study was approved by the University of Pittsburgh Institutional Review Board. Fifty-six (56) female subjects, 31 cases and 25 controls, 18 – 45 years of age, were recruited from the PI's ongoing longitudinal studies of BPD, from psychiatric outpatient clinics, and by advertisement from the surrounding community. The study was restricted to females as they comprise 75% of BPD patients in clinical settings, avoiding any confounds due to gender (DSM V, 2013). All subjects gave written informed consent. To be included in the BPD sample, subjects were required to meet criteria for a probable or definite lifetime diagnosis of BPD on the International Personality Disorders Examination (IPDE) (Loranger, 1999), and a definite current diagnosis of BPD on the Revised Diagnostic Interview for Borderline Patients (DIB-R), using a two-year timeframe (Zanarini et al., 1989). Co-morbidity on Axis I was determined by the Structured Clinical Interview for DSM-IV (SCID), for current and lifetime diagnoses (First et al., 2005). Healthy control subjects (HC) did not meet criteria for any current or lifetime Axis I or II disorders and were free of psychoactive medication. BPD subjects on psychoactive medication were permitted to remain on their medication. Immediately preceding the scan, all subjects had negative urine toxicology for drugs of abuse (MedTox) and negative pregnancy tests. Activation profiles from a subset of this sample, including both BPD and HC subjects, were previously reported (Soloff et al., 2015).

## Exclusion criteria

Exclusion criteria included: 1) a current or lifetime diagnosis of schizophrenia, delusional (paranoid) disorder, schizoaffective disorder, bipolar disorder, or psychotic depression; 2) a current diagnosis of Substance Dependence or any current drug and/or alcohol related CNS deficits. (A diagnosis of Substance Abuse was permitted so long as the subject had been abstinent for one week, showed no signs of withdrawal, and had a clean urine toxicology drug screen at the time of the scan.); 3) CNS pathology of any etiology, including acquired or developmental deficits or seizure disorder; 4) Physical disorders or treatments with known psychiatric consequence (e.g. hypothyroidism, steroid medications); 5) Mental Retardation (IQ <70 by WAIS); 6) standard exclusion criteria for MRI scans (i.e. ferromagnetic artifacts, inability to fit in the scanner, claustrophobia, inability to co-operate with instructions.)

## Imaging Specifications

Anatomical images were acquired on the 3.0T Siemens Trio system in the axial plane parallel to the AC-PC line using a 3D MPRAGE sequence (TE/TI/TR=3.29ms/900ms/2200ms, flip angle=9, isotropic 1mm<sup>3</sup> voxel, 192 axial slices, matrix size=256×192). fMRI data were acquired in the axial plane using gradient echo EPI (TR=2000 ms, TE=30 ms, flip angle=70 deg, 30 slices, slice thickness=3.1 mm, 3 mm x 3 mm in-plane, matrix size=64×64).

## fMRI paradigm

The Go No-Go test is a neuropsychological measure of response inhibition and motor impulsiveness that requires subjects to choose to respond (“Go”) or not respond (“No-Go”) based on target class. The typical Go No-Go paradigm targets impulsivity (but independent of emotional context) but using affectively neutral stimuli. Given our motivation to assess affective interference in the context of cognitive processing, we modified the traditional version of the paradigm. Only Ekman faces depicting negative (angry, sad, fearful), positive (happy), or neutral affect were deployed as stimuli (Ekman and Friesen, 1976; Soloff et al., 2015). Before a block of trials, subjects were instructed on which affective context in the upcoming block of rapidly presented faces would require a “Go” response (e.g., “Negative”). Subjects were instructed to make a response only if a presented face was consistent with the instructed affective context (e.g., “Go” for a Negatively valenced face, but “No-Go” for a positively valenced face). Thus, in gating responses to the affective valence of the Ekman faces, we intended for the task to induce an interaction between affective context, and cognitive processing in the specific domain of impulsivity.

During each block of trials, Ekman faces were presented briefly (500 ms) in a mixed jittered event-related design (Inter-Stimulus interval range: 500–1500 ms in 250 ms increments) (Amaro and Barker, 2006; Donaldson et al., 2001). As noted the affective context for target stimuli was signaled at block onset and subjects responded if the affect in the face was consistent with the affective context. In any given block, 67% of faces were targets (i.e., consistent with the signaled context, and required a “Go” response). Four block types were employed (three repetitions, 30 s block length): negative, neutral and positive valence and distorted blocks (in which target images were scrambled faces), with three fixation blocks interspersed. All responses were recorded by button press.

## fMRI processing

fMRI data were analyzed using SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). In all analyses, the first four images were discarded to account for EPI equilibration effects. The remaining images in the sequence were realigned to correct for head movements, corrected for slice timing, and subsequently spatially normalized according to the transformation matrix derived between the co-registered (to the mean EPI sequence image) T1-weighted image volume and the MNI template brain. The images were then smoothed spatially with a 3D Gaussian kernel of 6 mm FWHM and re-sampled ( $2 \times 2 \times 2 \text{ mm}^3$ ). A high-pass filter (cutoff 1/128 s) was employed to remove low-frequency signal drifts. The data were modeled voxel-wise, applying a general linear model (GLM) based on boxcar waveforms to conform to each of the negative, positive and neutral affective contexts, and convolved with the canonical hemodynamic response function. All subjects' head motion was within accepted limits ( $< 4 \text{ mm}$ ). Furthermore, in all first level models, the effects of motion were modeled by including the six motion parameters as covariates of no interest.

## PPI analyses

To assess the network profiles of the amygdala, psychophysiological interaction (PPI) was employed. PPIs are constructed by extracting a time-series from a seed region of interest and multiplying the activity with a stimulus function or regressor encoding the psychological context. For PPI modeling, first time series were extracted from *each participant* based on their first-level activation maps. To achieve this, first an effects of interest contrast ( $p < 0.05_{\text{FWE}}$ ) was used to statistically distinguish amygdala voxels that could be reliably classified as “signal” rather than “noise” or false-positives (Woodcock et al., 2016). This allowed us to identify the specify loci of amygdala activations based on a typically employed statistical filtering. The time series itself was the average signal from a sphere (2 mm radius) centered at the statistical peak within the amygdala's anatomical boundaries (Maldjian et al., 2003). This approach can be contrasted with approaches wherein the locus within a region is identified based on a second-level group map. We note that the current approach has a relative merit in that it respects *individual differences in activation peaks*, and enhances sensitivity for identifying peaks based on intra-subject maxima (Wadehra et al., 2013, Woodcock et al., 2016). Next, this time series was multiplied with three distinct contrasts each representing three separate affective contexts: These were, Negative > Positive, Neutral > Positive, Negative > Neutral. The positive weighting of the regressors modeled hypothesized “excitatory” modulation by the amygdala in the context of emotion processing (Phelps, 2006). The employed contrast structure allowed us to assess the relative hyper-modulatory effects of the amygdala across the spectrum of affective contexts (Positive to Negative)(Soloff et al., 2015). The intra-subject maps thus encode the strength of the interaction at the first level, and were submitted to separate (for each contrast) second level random effects analyses of co-variance, with group (HC vs. BPD) as the single factor, and age modeled as co-variate to accommodate age-differences between groups.

Significant differences (BPD – HC) were assessed using directional contrasts. Cluster level correction was employed to identify significantly different modulation by the amygdala by estimating the minimum cluster extent in order for modulated clusters to be rejected as false

positive (noise-only) clusters (Ward, 2000). This approach performs a Monte Carlo alpha probability simulation, computing the probability of a random field of noise (after taking into account the spatial correlations of voxels based on the image smoothness within each region of interest estimated directly from the data set), producing a cluster of a given size, after noise thresholding. The underlying principle is that true clusters will tend to occur over contiguous voxels within a region of relative functional homogeneity, whereas noise has much less of a tendency to form clusters of modulated voxels. A region-of-interest approach was used to focus analyses on anatomical structures of interest identified on the bases of previous studies. Thus, analyses were focused in a spatial mask that was derived from a combination of morphometric and fMRI analyses that has identified brain regions of clinical significance in BPD (Soloff et al., 2012; 2014, 2015). The network of anatomical regions is depicted in Supplementary Figure 1.

## Results

### Subject Characteristics

The mean (s.d.) age of the BPD sample was 30 (8.2) years, compared to 24.5 (5.5) years for healthy controls, ( $t$  3.00,  $df$  52.4,  $p$  = .004). At the time of the scan, current co-morbid Axis I diagnoses were noted in 27 BPD subjects (87.1%), the most frequent being MDD (in 19 subjects (61.3%)) and Generalized Anxiety Disorder (in 11 subjects (35.5%)), with some overlap. A current Substance Use Disorder was noted in only 2 subjects (6.5%). Additional Axis II co-morbidity was diagnosed in 18 BPD subjects (58.1%), the most frequent being Paranoid PD (in 5 subjects (16.1%)). Nineteen BPD subjects (61.3%) had histories of childhood abuse (14 sexually abused). Twenty-two (71%) BPD subjects had past histories of suicide attempts, 9 were non-attempters. Fifteen BPD subjects (48.8%) were taking one or more psychotropic medications: a.) antidepressants: venlafaxine (2), escitalopram (1), paroxetine (2), fluoxetine (2), sertraline (2), trazadone (1), citalopram (2), bupropion (2); b.) anxiolytics: clonazepam (1), alprazolam (1), lorazepam (2), hydroxyzine (2); c.) neuroleptics: aripiprazole (2), quetiapine XR (1); d.) mood stabilizers: topiramate (1), lamotrigine (2); e.) stimulants: methylphenidate (1).

### PPI Results (Table 1, Figures 1–3)

In the negative relative to the neutral affective context (Negative > Neutral), the amygdala exerted greater modulation of its targets in BPD compared to HC subjects in multiple areas. Voxel peaks were located in Rt. OFC, Rt. dACC, Rt. Parietal, Rt. Basal Ganglia, and Rt. dlPFC (in order of individual cluster extent) (Table 1). A small effect was also noted in Lt. amygdala. Results were remarkably similar in the Negative > Positive contrast, with greater modulation observed in Rt. OFC, Lt. dACC, Rt. Parietal, Rt. BG, and a small effect in Lt. amygdala. In the Neutral > Positive contrast, greater modulation in BPD than HC subjects was observed in two different OFC nodes (Lt. OFC, Rt. OFC), and a smaller area in L. Parietal cortex. HC subjects demonstrated greater amygdala modulation than BPD subjects only in the Neutral > Positive contrast, with activation in Lt. Parietal precuneus and a small area of Rt. OFC (medial orbital frontal cortex). The results suggest that across the spectrum of affective contexts, hyper-modulation in BPD observed the following ordering: Negative > Neutral > Positive.

Eleven (47.8%) of our BPD subjects were taking psychotropic medications, and medication use is a potentially confounding factor in fMRI studies of emotion processing (Schulze, et al., 2016). To test for medication effects on connectivity estimates, we compared connectivity parameters (that is, estimates of amygdala modulation) at the peak of each target. In investigating differences between medicated and non-medicated BPD participants, we found no differences in PPI parameter estimates. These null effects conform to our previously published results (Soloff et al., 2015), though we note that some meta-analyses report diminished activation of lt. amygdala and hippocampus among medicated subjects (Schulze, et al., 2016). While our BPD subjects were, on average, six years older than controls, age did not impact the results.

## Discussion

Using an affectively valenced Go No-Go task, we evaluated network profiles of the amygdala that might underpin affective interference in BPD compared to control subjects. Consistent with a model of “bottom up” arousal to emotional stimuli, the amygdala exerted hyper-modulatory effects on specific target regions that are relevant in processing response inhibition and motor impulsiveness. The resulting pattern of network dysfunction suggests that BPD subjects may be more vulnerable to affective interference because of amygdala hyper-modulation that increases with negative context.

The amygdala is involved in perception and production of emotion, especially the processing of fear, in both conscious and non-conscious awareness (Davidson et al., 1999, Williams et al., 2006). It assigns salience to incoming emotional stimuli, and, through extensive reciprocal anatomical connections to prefrontal cortex, including OFC and dACC, modulates the expression of emotion, and behavior (Tekin and Cummings, 2002, Barbas, 2007, Bonelli and Cummings, 2007). The OFC acts in concert with the dACC to broadly regulate attention, expression of affect and impulse. Response inhibition, (as assessed by Go No-Go), is a function of the OFC, and selectively engages the OFC in fMRI studies (Casey et al., 1997, Horn et al., 2003). The dorsal and mid-ACC, in concert with the OFC, are engaged by tasks involving conflict resolution (competing choices), error detection, and decision-making (Carter et al. 2000). In concert with the ventro-medial PFC, they are also involved in emotion regulation (Hazlett et al., 2005; Phillips, Ladouceur, & Drevets, 2008). We predicted that hyper-arousal of amygdala during negative affective stimulation would modulate activity in specific cortical regulatory nodes, including OFC and dACC. In a negative affective context, hyper-activation of amygdala in BPD subjects is accompanied by diminished activation of OFC, and impaired behavioral performance, compared to healthy controls (Silbersweig et al., 2007). In a PET study, New et al. (2007) demonstrated diminished metabolic connectivity between amygdala and the OFC in patients with BPD, suggesting a functional vulnerability to disinhibited emotion and behavior. Greater modulation in BPD compared to control subjects between the amygdala, OFC and dACC during response inhibition under negative affective conditions may also reflect a relative decrease in strength of tonic cortical inhibition on limbic arousal. In the clinical context, diminished cortical inhibition during episodes of negative affective stress in BPD patients lowers the threshold for emotional and behavioral dyscontrol (Siever, 2008).



BPD subjects, compared to HC, also have increased amygdala modulation of the OFC in response to the neutral (> positive) affective condition. In fMRI studies, BPD subjects tend to project negative attributes onto neutral faces, and experience hyper-arousal of amygdala compared to healthy controls in response to neutral Ekman faces (Donegan et al., 2003).

Increased modulation by the amygdala of the parietal cortex/precuneus in BPD subjects may reflect a heightened response to specific task demands of the affective Go No-Go paradigm, especially the processing of visuo-spatial inputs and spatial attention. Increased modulation by the amygdala of the parietal cortex in HC subjects compared to BPD in the neutral condition, suggests a basic role for parietal cortex in task performance. The posterior parietal cortex is part of the central executive network. In concert with the dPFC, posterior parietal cortex is involved in rule based problem solving and decision making in the context of goal directed behavior (Menon, 2011). In the presence of negative affect, increased modulation by the amygdala of the parietal cortex in BPD may contribute to affective interference with task performance (Cavanna and Trimble, 2006).

Similarly, increased modulation of the basal ganglia (BG) in BPD compared to HC under negative affective conditions may reflect specific task demands requiring attention and reward-based decision-making, which are functions of the BG (Herrero et al., 2002, Voytek and Knight, 2010). Impulsive decision-making, and even suicidal behavior, have been associated with structural deficits in the BG (Vang et al., 2010, Dombrovski et al., 2012). Both parietal cortex and BG were activated in fMRI studies comparing BPD to HC subjects on the affective Go No-Go task (Soloff et al., 2015).

### **Cognitive defenses against affective interference**

The “top down/bottom up” hypothesis of emotion regulation is supported by studies of cognitive defenses against affective interference in healthy subjects and patients with BPD. Cognitive defenses against affective interference include voluntary reappraisal, suppression and distancing techniques, and involuntary habituation. In fMRI studies involving healthy subjects, cognitive reappraisal and distancing in response to aversive stimuli are associated with increased cortical and decreased limbic activation (Koenigsberg et al., 2010, Schulze et al., 2011, Banks et al., 2007). In contrast, among BPD subjects, voluntary efforts at distancing emotional response to negative social cues are associated with failure to down-regulate amygdala or to activate cortical regulatory centers compared to controls (Koenigsberg et al., 2009). In a study of voluntary, effortful down-regulation of negative emotional responses to aversive IAPS scenes, BPD subjects showed decreased activity in the lt. OFC and increased activation in the insula, bilaterally (Schulze et al., 2011). Difficulties in emotion regulation during cognitive reappraisal were positively associated with insular activation and negatively associated with activity in the OFC (Schulze et al., 2011). PPI studies of voluntary cognitive reappraisal in healthy subjects report increased amygdala-frontal coupling (Banks et al. 2007).

In implicit habituation paradigms, healthy subjects demonstrate diminished emotional responses with repeated exposure to negative pictures, PPI analyses reveal increased insula-amygdala coupling associated with greater success in habituation (Denny et al., 2014). Among subjects with BPD, fMRI studies using the habituation paradigm demonstrate

diminished activation in dACC and temporal gyri during repeated negative pictures, and increased activation in amygdala and insula (Koenigsberg et al., 2014). PPI analyses of habituation trials among subjects with BPD demonstrate diminished coupling of Lt. mid-posterior insula with amygdala bilaterally compared to healthy controls. Increases in coupling were associated with greater behavioral habituation (Koenigsberg et al., 2014).

Successful treatment in BPD depends, in part, on diminishing affective instability. Dialectical Behavior Therapy (DBT) is a cognitive behavioral treatment directed at enhancing emotion regulation in patients with BPD (Linehan, 1993). A one year treatment study of DBT in non-medicated patients with BPD produced normalization of amygdala hyper-reactivity to provocative IAPS pictures relative to healthy control subjects. Decreased reactivity of amygdala following DBT was associated with improved emotion regulation (Goodman et al., 2014).

Using the affectively valenced Go No-Go paradigm, these network-based analyses by PPI show greater differences between BPD and HC subjects than studies using conventional fMRI methods (Soloff et al., 2015). This increased sensitivity suggests that PPI network profiles more closely approximate brain network interactions, and provide a more meaningful assessment of dysfunctional neurobiology in psychiatric conditions (Friston et al., 1997; J. X. O'Reilly, M. W. Woolrich, T. E. J. Behrens, S. M. Smith, & H. Johansen-Berg, 2012). This increase in sensitivity appears even though PPI analyses constitute relatively limited models of network interactions. i.e. PPI models capture statistical dependencies between signals in the seed and its targets depending on the psychological context (Silverstein et al., In Press, Stephan, 2004). The choice of seed and the psychological context are free parameters of the model, and are chosen based on prior knowledge regarding task characteristics and the putative network relationships of the seed (Friston et al., 1997; Horwitz et al., 2005; Wadehra, Pruitt, Murphy, & Diwadkar, 2013; Woodcock et al., 2016). PPIs constitute a model of directed functional connectivity and are distinguishable from more sophisticated models of brain network function (e.g., dynamic causal models) that provide estimates of effective connectivity, or causal interactions exerted between neuronal populations (Friston et al., 2012; Diwadkar et al., 2014; Jagtap & Diwadkar, 2016). Given our focus on assessing “bottom-up” network profiles in BPD, the amygdala was a logical choice of seed. Additional seeds or psychological contexts would add complexity to our network model.

The BPD patient is vulnerable to emotion dysregulation, and to affective interference with cognitive functioning. These aberrant behaviors arise from discoverable interactions in the neural substrate and are related to dysfunctional brain networks. The vulnerability of BPD subjects to affective interference with impulse control may be due to specific network dysfunction related to amygdala hyper-arousal and its effects on prefrontal regulatory regions such as the OFC and dACC.

## Limitations

A limitation of our approach was that the choice of seed was agnostic with respect to the sub-divisions of the amygdala. The amygdala is composed of functionally variegated clusters of nuclei (Pitkanen & Amaral, 1998) but their identification using MRI depends on

high-resolution techniques (Hrybouski et al., 2016) or as we have previously shown (Barbour et al., 2010), approximations based on maximum probability maps of the structure's sub-nuclei. In our analyses, the choice of seed was statistically motivated, and it is expected that the locations of statistically significance peaks (see Methods) are subject to inter-participant variability. Thus we are unable to (and do not) make claims regarding the specific anatomical pathways that might underpin the patterns of amygdala modulation that we reveal. Rather, our results speak to the functional transactions from the amygdala to its targets in the context of our task (Silverstein et al., 2016; Friston, 2011), and how these functional transactions are distorted in BPD.

We chose to study women with BPD because of the preponderance of women subjects with BPD compared to men in a clinic setting. However, gender differences in the borderline patient's response to emotional stimuli, especially aggressive responses to negative stimuli, limit generalization of our results. e.g. Women with BPD tend to internalize reactive aggressive feelings (as in self-injury), while men with BPD tend to externalize aggression (as in antisocial behaviors) (Johnson et al., 2003). Such gender differences may result in differing fMRI activation patterns.

We also used healthy control subjects to compare to our BPD sample, introducing uncontrolled variables associated with BPD such as diagnostic co-morbidities, adverse life experiences (e.g. childhood abuse), and medication use. These uncontrolled variables could potentially confound results. The use of a clinical control group could reduce, though never fully eliminate, this limitation to interpretation.

The use of medication in nearly half of our BPD subjects poses an additional limitation to interpretation. All of our BPD subjects were currently symptomatic, and were seen in an ambulatory setting. We assessed the effects of medication use on activation metrics among our BPD subjects by comparing medicated to non-medicated subjects; however, this comparison is relatively underpowered and might not identify such effects if they existed.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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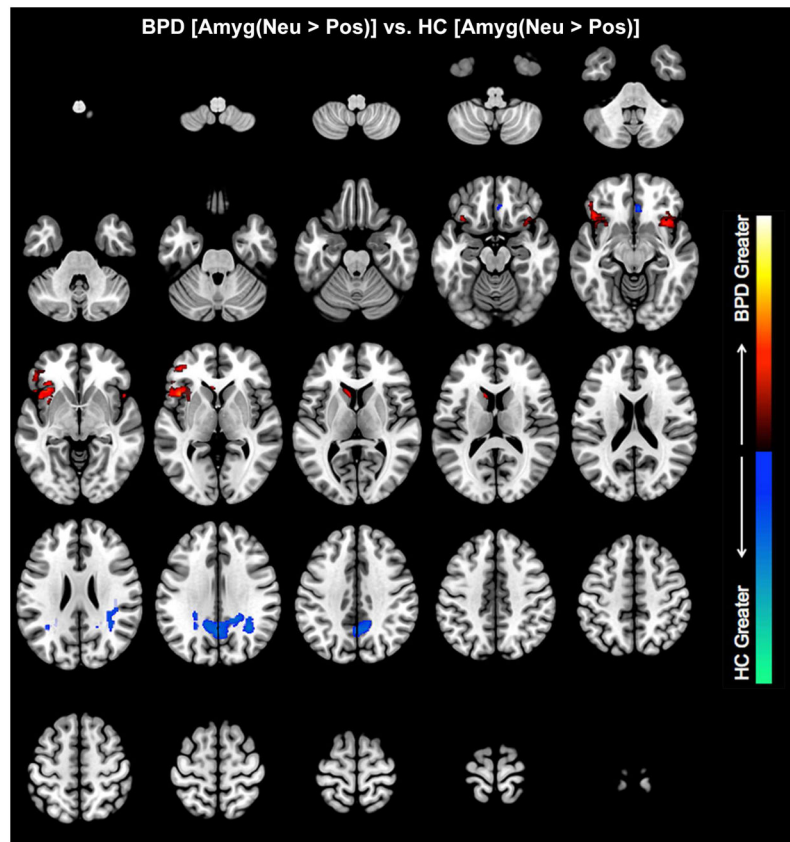
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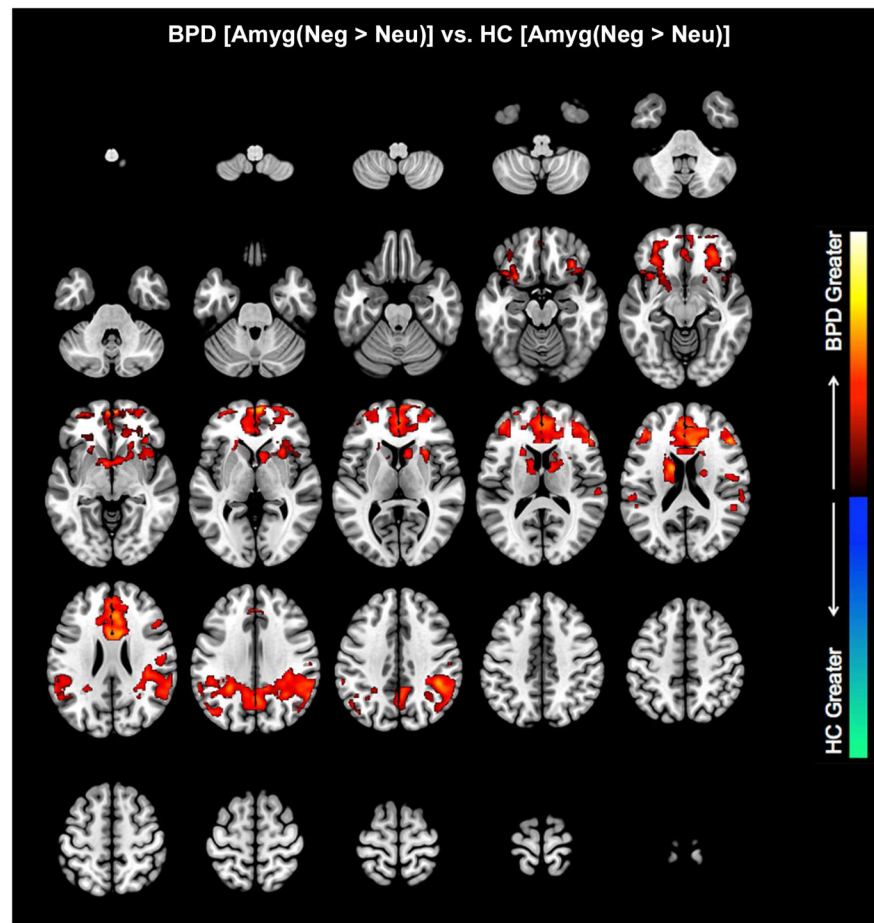


### Highlights

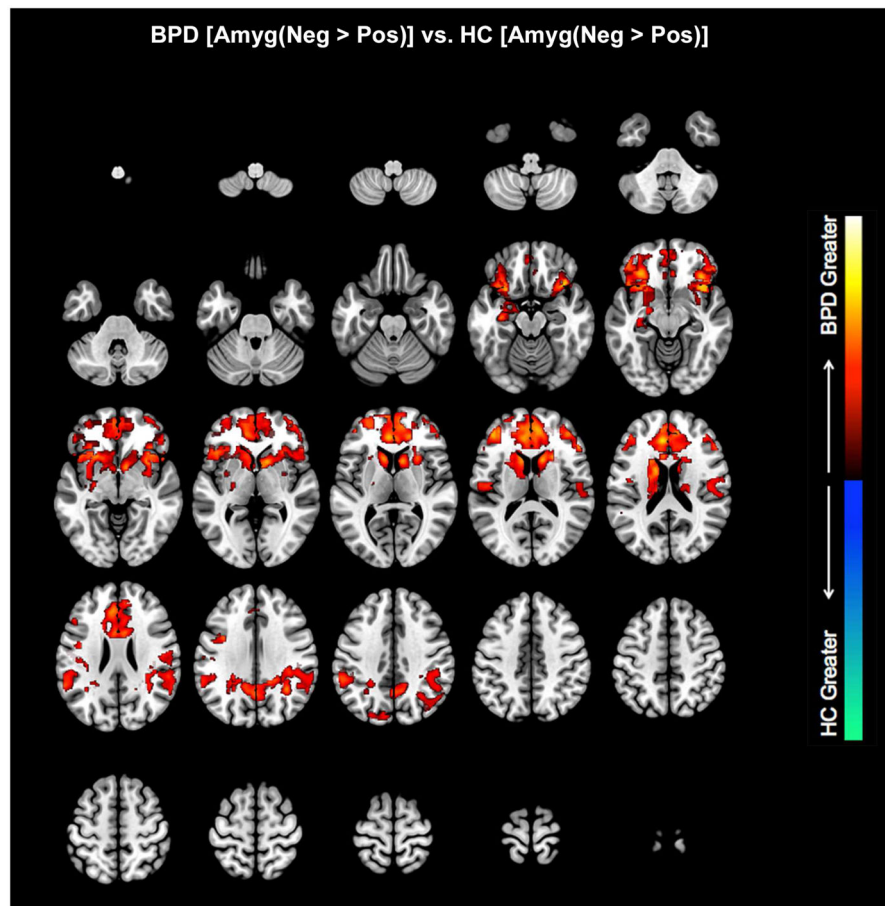
- Emotion dysregulation in BPD may result from an imbalance in fronto-limbic network function.
- PPI analysis demonstrated network dysfunction in BPD during an affective Go No-Go task.
- In the negative condition, amygdala exerted greater modulation of its targets in BPD compared to HC subjects.
- Amygdala modulation was greatest in regions relevant for processing response inhibition.
- BPD vulnerability to affective interference with cognition is related to underlying dysfunctional brain networks.



**Figure 1.** Neutral relative to positive conditions. Clusters depict where the amygdala differentially modulates brain regions in BPD and HC (see Table 1 for statistical and location information). BPD were characterized by increased amygdala modulation of the bilateral orbitofrontal cortex, whereas in HC, we observed increased modulation of the parietal cortex.



**Figure 2.** Negative relative to Neutral conditions. Clusters depict where the amygdala differentially modulates brain regions in BPD and HC (see Table 1 for statistical and location information). No effects were observed for HC, However, BPD were characterized by increased amygdala modulation of a large network of frontal, cingulate and parietal regions, with the effects more pronounced than those observed comparing neutral to positive contexts.



**Figure 3.** Negative relative to Positive conditions. Clusters depict where the amygdala differentially modulates brain regions in BPD and HC (see Table 1 for statistical and location information). Again, BPD were characterized by increased amygdala modulation of a large network of frontal, cingulate and parietal regions.

**Table 1**

Amygdala modulation under three affective conditions during the Go No-Go task

Anatomical ROI	Contrast	Ind. Cluster Ext.	p uncorrec.	Voxel Peak (MNI)
A. Neg > Neu				
Amygdala	BPD>HC	160	0.002	-28 0 -14 - L-Amygdala
Basal Ganglia	BPD>HC	2681	<0.001	34 10 -6 - R-BG
dACC	BPD>HC	6005	<0.001	9 12 27 - R-dACC
OFC	BPD>HC	9600	0.001	38 20 -15 - R-OFC
Parietal	BPD>HC	2939	<0.001	46 -15 22 - R-Parietal
dPFC	BPD>HC	651	<0.001	46 28 21 - R_DLPFC
B. Neu > Pos				
OFC	BPD>HC	677	<0.001	36 15 -15 - R-OFC
OFC	BPD>HC	1022	<0.001	-42 14 0 - L-OFC
<u>Parietal</u>	<u>BPD&gt;HC</u>	<u>170</u>	<u>0.005</u>	<u>-56 -48 39 - L-Parietal</u>
Parietal	HC>BPD	1188	0.005	2 -57 33 - L-Precuneus
OFC	HC>BPD	62	0.008	6 33 -15 R-Med Orb Frontal
C. Neg > Pos				
Amygdala	BPD>HC	165	0.002	-28 0 -14 - L-Amyg
Basal Ganglia	BPD>HC	2681	<0.001	34 10 -6 - R-BG
dACC	BPD>HC	6621	<0.001	-6 34 18 - L-dACC
OFC	BPD>HC	9640	<0.001	38 20 -15 - R-OFC
Parietal	BPD>HC	2939	<0.001	46 -15 22 R-Parietal