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## Dialectical behavior therapy alters emotion regulation and amygdala activity in patients with borderline personality disorder

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### Abstract

**Objective**—Siever and Davis' (1991) psychobiological framework of borderline personality disorder (BPD) identifies affective instability (AI) as a core dimension characterized by prolonged and intense emotional reactivity. Recently, deficient amygdala habituation, defined as a change in response to repeated relative to novel unpleasant pictures within a session, has emerged as a biological correlate of AI in BPD. Dialectical behavior therapy (DBT), an evidence-based treatment, targets AI by teaching emotion-regulation skills. This study tested the hypothesis that BPD patients would exhibit decreased amygdala activation and improved habituation, as well as improved emotion regulation with standard 12-month DBT.

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#### Conflict of interest

None of the authors have any biomedical financial interests or potential conflicts of interest to declare.

#### Contributors

**Marianne Goodman** – Dr. Goodman was the study PI and responsible for all aspects of the study.

**David Carpenter** – Dr. Carpenter was responsible for image analysis under Dr. Hazlett's supervision.

**Cheuk Y. Tang** – Dr. Tang was responsible for all aspects of fMRI acquisition.

**Kim E. Goldstein** – Dr. Goldstein assisted with the coordination and collection of healthy control and patient data.

**Jennifer Avedon** – Ms. Avedon was responsible for study implementation, recruitment of the healthy controls, and patient data collection.

**Nicolas Fernandez** – Mr. Fernandez was tasked with data collection and assisted in data analysis.

**Kathryn A. Mascitelli** – Ms. Mascitelli helped with data coordination and organization of the database for this study.

**Nicholas J. Blair** – Mr. Blair helped with the manuscript preparation including references and formatting of the figures and table.

**Antonia S. New** – Dr. New was a study design mentor for the Career Development award that partially funded this study.

**Joseph Triebwasser** – Dr. Triebwasser assisted with patient data collection.

**Larry J. Siever** – Dr. Siever assisted with the study design, and was the primary mentor for the Career Development award that partially funded this study.

**Erin A. Hazlett** – Dr. Hazlett was responsible for overseeing all aspects of the fMRI component of the study, conducting the statistical analyses, and write-up of the Results section. She was a mentor on Dr. Goodman's Career Development award that partially funded this study.

**Methods**—Event-related fMRI was obtained pre- and post-12-months of standard-DBT in unmedicated BPD patients. Healthy controls (HCs) were studied as a benchmark for normal amygdala activity and change over time ( $n = 11$  per diagnostic-group). During each scan, participants viewed an intermixed series of unpleasant, neutral and pleasant pictures presented twice (novel, repeat). Change in emotion regulation was measured with the Difficulty in Emotion Regulation (DERS) scale.

**Results**—fMRI results showed the predicted Group  $\times$  Time interaction: compared with HCs, BPD patients exhibited decreased amygdala activation with treatment. This post-treatment amygdala reduction in BPD was observed for all three pictures types, but particularly marked in the left hemisphere and during repeated-emotional pictures. Emotion regulation measured with the DERS significantly improved with DBT in BPD patients. Improved amygdala habituation to repeated-unpleasant pictures in patients was associated with improved overall emotional regulation measured by the DERS (total score and emotion regulation strategy use subscale).

**Conclusion**—These findings have promising treatment implications and support the notion that DBT targets amygdala hyperactivity—part of the disturbed neural circuitry underlying emotional dysregulation in BPD. Future work includes examining how DBT-induced amygdala changes interact with frontal-lobe regions implicated in emotion regulation.

## Keywords

Borderline personality disorder; Emotion regulation; Amygdala; Habituation; fMRI

## 1. Introduction

Borderline Personality Disorder (BPD) affects 2% of the population and is characterized by impulsivity and poor affect regulation (Links et al., 1998), and severe morbidity and mortality, including reported suicide rates 50 times the general population (Skodol et al., 2002). BPD patients experience more frequent psychiatric hospitalizations, greater use of outpatient psychotherapy and emergency room use than individuals with any other psychiatric disorder (Bender et al., 2001; Lieb et al., 2004b).

Affective Instability (AI) is responsible for the considerable morbidity across psychiatric disorders including aggression, suicidality, and disrupted relationships. AI is defined as “rapid and reactive oscillations of intense affect, with a difficulty in regulating these oscillations or their behavioral consequences” (Marwaha et al., 2013). It is further characterized by heightened intensity of affect, usually in negative valence, rapid affective shifts lasting minutes to hours, hypersensitivity to environmental triggers, usually interpersonal in nature and, dysregulated affect modulation (Koenigsberg, 2010; Renaud and Zacchia, 2012; Carpenter and Trull, 2013; Links et al., 2008). AI contrasts with the affective/mood dysregulation seen in major depression and bipolar disorder where the mood disorder is sustained for days to weeks and relatively autonomous of environmental triggers.

While AI is expressed in other disorders, AI is at the core of BPD and subsumes many of the diagnostic criteria including affective lability, intense anger, chronic emptiness and behaviors like suicide and self-mutilation that may reflect misguided efforts to modulate strong and aversive emotional states (Linehan, 1993). Siever and Davis’ (1991)

psychobiological approach to the understanding of personality disorders highlights the dimension of AI in BPD.

Linehan's Biosocial Theory (1993) conceptualization of emotional dysregulation in BPD, overlaps with the construct of AI and delineates two components: a) heightened emotional responsivity characterized by high sensitivity to emotional stimuli and heightened emotional intensity, and b) difficulties in effortful modulation of negative affect. The emotional hyper-responsivity is postulated to be biologically mediated, arising from genetic vulnerabilities, intrauterine and/or early childhood events that interact with an "invalidating" environment (Linehan, 1993), as is supported by multiple studies indicating high rates of childhood trauma and neglect in this population (Fossati et al., 1999; Goodman et al., 2004). Empirical research on emotional hyper-responsivity in BPD includes subjective reports of heightened affective experiences to various emotional stimuli such as films, audiotapes, and pictures from the International Affective Picture System (IAPS) (Arntz et al., 2000; Herpertz et al., 1999; Yen et al., 2002). More recently, the use of objective psychophysiological parameters including affective startle modulation, skin conductance, and heart rate measures of emotional arousal have been employed, also revealing heightened responsivity in BPD, e.g., (Hazlett et al., 2007; Herpertz and Koetting, 2005). The second part of Linehan's Biosocial Theory focusing on difficulties in effortful modulation of negative affect is supported by neuroimaging data demonstrating inefficient regulatory control of the amygdala by prefrontal cortex (PFC) regions (Lis et al., 2007; Minzenberg et al., 2007; Wingenfeld et al., 2009; Silbersweig et al., 2007) and dysfunctional coupling of fronto-limbic structures (New et al., 2007).

Building on the substantial literature in both animals and humans that implicates amygdala in emotional processes, including the perception and production of emotion (Davidson et al., 1999), there is growing evidence supporting the role of amygdala in the emotion processing disturbances observed in BPD. Functional magnetic resonance imaging (fMRI) studies in BPD show increased amygdala activity to specific types of stimuli, e.g., "unresolved" life events (Schmahl et al., 2006), emotional faces (Donegan et al., 2003), positive and negative emotional pictures (Herpertz et al., 2001) and emotionally-triggering scripts (Beblo et al., 2006).

More recently, our group has demonstrated exaggerated amygdala response to repeated emotional pictures in two separate BPD studies. The first, in the largest sample size of unmedicated BPD patients ( $n = 33$ ) studied with fMRI to date (Hazlett et al., 2012) were compared with healthy controls (HC) and schizotypal personality disorder (SPD) patients while viewing socially-relevant IAPS pictures. The main finding was that compared with the other two groups, BPD patients failed to show amygdala habituation to repeated emotional (unpleasant and pleasant) but not neutral pictures. The second study, (Koenigsberg et al., 2014), using a similar IAPS habituation paradigm but an avoidant personality disorder psychiatric-control group, examined functional connectivity differences between groups. The BPD group showed greater amygdala activity to unpleasant pictures collapsed across novel and repeated conditions compared with both the HC and avoidant groups and less functional connectivity between the midposterior insula and the left and right amygdala relative to the HC group (Koenigsberg et al., 2014). Taken together, these findings suggest

that affective instability in BPD may be mediated by an overactive amygdala that manifests as increased emotionality, sensitivity and slow return to baseline.

In addition to functional differences in amygdala activity, some (Driessen et al., 2000; Tebartz van Elst et al., 2003) but not all (Goldstein et al., 2009; Rusch et al., 2003) structural MRI studies report significantly smaller amygdala volumes in BPD patients compared with HCs, with discrepant findings possibly due to posttraumatic stress disorder (PTSD) comorbidity (de-Almeida et al., 2012).

Dialectical Behavior Therapy (DBT) emphasizes the role of emotion regulation (Bohus et al., 2004; Linehan et al., 1991) and targets the acquisition of skills and techniques to encourage cognitive control over maladaptive behavioral patterns (Neacsiu et al., 2010). It has achieved widespread proliferation due to its robust empirical basis and exportability and is included as a component of the APA Practice Guideline for the treatment of BPD. With over 17 randomized clinical trials, DBT is the psychotherapy approach for BPD with the largest empirical base, however, minimal data exists regarding neurobiological mechanisms of change with DBT, or the existence of specific predictors for positive treatment response (Kleindienst et al., 2011) that might guide clinician treatment decisions.

While neuroimaging and psychophysiological studies of a psychotherapeutic treatment have been conducted in major depressive disorder (MDD) (Brody et al., 2001; Goldapple et al., 2004; Mayberg, 2003), few such studies exist in BPD. A small neuroimaging pilot on DBT (Schnell and Herpertz, 2007) highlights the role of amygdala normalization. This study scanned six BPD and six HC participants at five time points over a 12-week inpatient DBT program, with an IAPS paradigm. DBT treatment response was not operationalized but rather was defined as whether two of three treatment goals were met. DBT treatment decreased activity in anterior cingulate cortex (ACC), posterior cingulate, and insula to unpleasant stimuli. DBT responders (four of six) also demonstrated diminished activation in left amygdala and bilateral hippocampus (Schnell and Herpertz, 2007).

The present study examines DBT treatment effect on emotion regulation in unmedicated outpatients with BPD as measured by changes in the Difficulties in Emotion Regulation Scale (DERS) (Gratz and Roemer, 2004) and uses an emotional processing task to investigate amygdala changes after a standard 12-month course of DBT. A yoked HC group was included as a benchmark for normal amygdala activity and change over 12 months. Given our prior finding of exaggerated amygdala response and impaired habituation to unpleasant pictures in BPD, this investigation focused on the effects of DBT on the amygdala—our *a priori* region of interest. Individual differences in treatment response were also examined with correlations between the change in emotion regulation as measured by the DERS and amygdala activity from pre- to post-DBT treatment. Lastly, we examined change in emotion regulation with the DERS, independent of the amygdala as well, comparing baseline, 6, and 12 months. We hypothesized that the BPD patients would show a decrease in amygdala reactivity following treatment, and that the magnitude of this change would be associated with improved emotion regulation as measured by the DERS. In contrast, we hypothesized that the HC group would show consistent amygdala activation

over time and their emotion regulation scores on the DERS would also remain stable over time (i.e. baseline, 6 months, 12 months).

## 2. Methods

### 2.1. Participants

Twenty-two age- and gender-matched unmedicated BPD and HC participants (11 in each group) were included in this study (Table 1). All eligible participants received a full diagnostic structured interview which included the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (First et al., 1996a) and the Structured Interview for DSM-IV Personality Disorders (SIDP) (First et al., 1996b) conducted by a clinical psychologist specifically trained in the assessment of Axis II disorders. Weekly consensus and diagnostic meetings were led by a second clinical psychologist or research psychiatrist. In our laboratory, the intra-class correlation for BPD diagnosis is 0.80. All patients met DSM-IV criteria for BPD. HCs had no Axis I or II disorder, or family history of an Axis I disorder.

Exclusion criteria for all participants included severe medical or neurological illness, head injury, or substance dependence or abuse during the prior six months. All participants had a negative urine toxicology screen for drugs of abuse during the study's screening visit and on each fMRI scan day, women also had a negative pregnancy test on each scan day. Exclusion criteria for patients included meeting DSM-IV criteria for any schizophrenia-related psychotic disorder, bipolar (Type I) disorder, or current MDD (no episode in the prior 6 months). Patients were excluded if they had a history of a suicide attempt, or inpatient psychiatric hospitalization within the past six months as required by the local IRB for safety concerns given that concurrent psychoactive medication was not allowed in this study. Written informed consent approved by the Institutional Review Board was provided by all participants.

In addition to the DERS, symptoms were also assessed during the DBT trial using the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) (Frankenburg and Zanarini, 2002), Hamilton Depression Rating Scale (Hamilton, 1960), and Positive and Negative Affective Scale (PANAS) (Watson et al., 1988).

### 2.2. DBT treatment

The BPD patients received standard 12-month DBT treatment, including weekly skills training group (90 min), weekly individual treatment (50–60 min) and telephone coaching as needed. DBT therapists participated in a weekly 60-min consultation meeting. DBT therapists were experienced Ph.D. or M.D. clinicians who received intensive 10-day training. Individual DBT therapists were rated for adherence on taped sessions and judged by members of the Linehan research group. Adherence monitoring for research participants who agreed to videotaping included review of the initial two tapes for any therapist-patient dyad and random tapes ranging from 6 to 8 week intervals for the remainder of the year-long treatment. Adherence ratings ranged from 3.7 to 4.2. Any rating <4 was reviewed in weekly consultation meetings.

### 2.3. Event-related fMRI task measuring emotion processing

The fMRI task employed in this study was identical to the one previously published in a larger study of BPD patients (Hazlett et al., 2012). During the fMRI scan, participants viewed unpleasant, neutral, and pleasant photographic pictures from the IAPS (Lang and Bradley, 2007; Fig. 1). A total of 96 intermixed unpleasant, neutral, and pleasant photographic images were presented using E-Prime software (Psychology Software Tools, Pittsburgh, Pennsylvania) (Schneider et al., 2002) in the scanner. The 96 pictures were presented twice within their respective run, for a total of 192 picture trials. Participants were instructed to attend to the picture the entire time it was presented and think about the meaning for them personally. Immediately following the offset of each picture, a cartoon-like picture of a right hand with the pointer finger labeled as pleasant, middle finger labeled as neutral, and the ring finger labeled as unpleasant appeared for 2 s. As soon as participants saw the hand prompt, they made a three-choice response with their right hand using a BrainLogics fiber optic button system (Psychology Software Tools, Inc., Pittsburgh, Pennsylvania). The responses following each picture were recorded on a desktop computer and helped to ensure that participants were continuously engaged in the task. Immediately following the scan, participants viewed the same 96 pictures again outside the magnet on a laptop and rated them using the Self-Assessment Manikin scale (9-point scale) (Bradley and Lang, 1994).

Of the 192 picture trials, each was 8 s long and included either the presentation of a picture (for 6-s) followed by a three-choice button press response prompt (for 2 s; described in detail below) or a fixation cross (8 s) in a 3:1 ratio. The presentation of either a picture or fixation cross was semi-randomized, with the number of consecutive trials varying from one to six for pictures and one to three for fixation trials. Each run contained 24 unique pictures (8 unpleasant, 8 neutral, 8 pleasant) that were repeated once (48 picture events), and 16 non-picture (fixation cross) events (total = 64 contiguous trials per run). The total scan time was 38-min and 12-s, which was divided into four runs, with 30-s before and 31-s after each run ( $30 + [8 \times 64] + 31 = 573$  s; four runs = 2292 s).

We chose predominantly social pictures, including faces and social interactions. Across the four runs, the unpleasant and pleasant pictures were matched based on the standardized picture ratings from the IAPS manual for arousal level (all  $p > 0.28$ ). They were equally divergent from neutral in terms of valence. The neutral pictures were matched across each of the four runs on low arousal and neutral valence levels. All participants viewed the same stimulus sequence.

### 2.4. MRI image acquisition

The MRI scan procedure was conducted on a Siemens Allegra head-dedicated 3T scanner and included a T2 scan, EPI scan and a T1-weighted structural MP-RAGE (Magnetization Prepared Rapid Gradient Echo scan). The T2 involved a Turbospinecho sequence (TE = 99 ms, TR = 5760, Slice thickness = 3 mm/skip 1 mm, FOV = 21 cm, matrix  $256 \times 256$ , 32 slices). EPI images were acquired with a BOLD-EPI sequence (42 axial slices, 2.5 mm thick, skip = 0.8 mm (33%), TR = 3000 ms, TE = 27 ms, flip angle =  $85^\circ$ , FOV = 210 mm, matrix =  $64 \times 64$ ). For high resolution structural images, we acquired T1-weighted structural



MP-RAGE imaging (208 slices for whole brain; axial acquisition, 0.82 mm slice thickness, TR = 2500 ms, TE = 4.38 ms, TI = 1100 ms, flip angle = 8°, FOV = 210 mm, matrix size = 256 × 256 × 208).

## 2.5. Image processing

FSL's (Smith et al., 2004) fMRI Expert Analysis Tool (FEAT) was used for image processing. The fMRI data were preprocessed with motion correction using MCFLIRT (Jenkinson et al., 2002), non-brain removal using BET (Smith, 2002), spatial smoothing (FWHM = 5 mm) and a high-pass temporal filter (cutoff = 70 s).

## 2.6. Amygdala region-of-interest analysis

For each participant, the MP-RAGE and EPI images were co-registered with a 7-degrees-of-freedom (DOF) linear transformation followed by alignment to the MNI brain template using a 12-DOF linear fit. Following preprocessing, a general linear model (GLM) was used at a first-level analysis including the following explanatory variables (EVs) for six key stimulus conditions: unpleasant/novel, unpleasant/repeated, pleasant/novel, pleasant/repeated, neutral/novel, and neutral/repeated averaged across the blocks/runs. We obtained the mean time series averaged across the voxels of the right and left amygdala region-of-interest (ROI) defined by the Talairach atlas implemented in FSL. Mean BOLD activation within the amygdala ROI using FEAT and FSL's Feat-Query tool were calculated for each of the six conditions. The units of measurement for amygdala activation was % activation [z-scores].

## 2.7. Statistical analysis

Statistica (StatSoft, 2010) was used to conduct a multivariate ANOVA for amygdala activation: Group (HC- vs. -BPD) × Time (0, 12 months) × Picture type (U,N,P) × Picture repetition (novel, repeated) × Hemisphere (left, right). For the MANOVA, Diagnostic Group was the between-group factor and the remaining factors were all repeated measures. Multivariate F-values (Wilks Lambda) are reported. Significant interaction effects with Diagnostic Group were followed up with Fisher's-LSD tests to determine the direction of the interaction.

We also examined between-group changes in emotion regulation over time using the Difficulty in Emotion Regulation Scale (DERS) total scores at baseline, 6 and 12 months using a Group × Time (0, 6, 12 months) MANOVA. In order to examine the association between changes in amygdala activation (during unpleasant, repeated pictures) and emotion regulation (total DERS score and the DERS Strategy subscore), Pearson correlation coefficients were conducted on change scores (0 minus 12 months). A positive DERS change score reflects improvement in emotion regulation.

In order to determine whether subthreshold depressive symptoms were a possible confound in this BPD sample and should be used as a covariate in our ANOVAs, we examined the relationship of subthreshold depressive symptoms in the BPD patients and amygdala activation. A correlation between HAM-D change scores and amygdala activation difference scores (0–12 months) for repeated unpleasant pictures was conducted and it was not

significant,  $r = -0.05$ ,  $p > 0.87$ . Given that depression did not correlate with our primary dependent variable, amygdala change, we did not use ANCOVA.

### 3. Results

We report on 11 BPD subjects who completed 12 months of DBT treatment and pre/post fMRI. While 16 subjects finished the 12 month DBT trial, 5 participants were unable to complete the imaging paradigms for various reasons including claustrophobia ( $n = 2$ ), acquisition of metal braces for teeth ( $n = 1$ ), diagnosis of metastatic cancer ( $n = 1$ ), refusal of scan ( $n = 1$ ).

#### 3.1. Self-report of difficulties in emotion regulation (DERS)

We examined the DERS total scores for the HC and BPD groups at baseline (0), 6 months, and 12 months. The DERS scores were stable over time for the HC group and in contrast, showed a decline with DBT treatment in the BPD group, Group  $\times$  Time interaction,  $F[2,36] = 3.71$ ,  $p < 0.04$ , H-F, epsilon = 1.00,  $\eta^2 = 0.21$  (Fig. 2). The main effect of Group was also significant reflecting higher overall total DERS scores in the BPD group compared with the HCs,  $F[1,18] = 32.39$ ,  $p < 0.0001$ . The main effect of Time was also significant, primarily reflecting the overall decline across time in DERS scores for patients,  $F[2,36] = 7.09$ ,  $p < 0.003$ .

#### 3.2. fMRI

The HC group showed overall amygdala activation (averaged across picture type, hemisphere, and novel/repeated pictures) that was similar at baseline and 12 months, whereas the BPD group exhibited an overall decrease in amygdala activation post-treatment, Group  $\times$  Time interaction,  $F[1,20] = 4.89$ ,  $p < 0.04$ ;  $\eta^2 = 0.24$ , HC  $>$  BPD post-hoc,  $p < 0.08$ , trend level, Fig. 3). In order to confirm that BPD patients showed a change (i.e. decrease) in amygdala activity with DBT while the HC group showed no change over 12 months, we followed-up this significant interaction effect with post-hoc  $t$ -tests examining the amygdala change scores (0–12 months) for each group (compared to 0) and between-group differences. The results indicated that the HC group did not show a significant change in amygdala activity over time, whereas the BPD group did (0–12 month difference scores: HC:  $1.99 \pm 16.67$  (vs. 0,  $p = 0.70$ ) vs. BPD:  $-11.54 \pm 11.73$  (vs. 0,  $t(10) = 3.26$ ,  $p < 0.01$ ); (Cohen's  $d = 0.95$ ), and this between-group difference was significant,  $t(20) = 2.20$ ,  $p < 0.04$ .

There was also a significant for Group  $\times$  Time  $\times$  Picture type  $\times$  Picture repetition  $\times$  Hemisphere interaction,  $F[2,19] = 3.71$ ,  $p < 0.05$ ,  $\eta^2 = 0.16$ , Fig. 4. Compared with healthy controls, individuals with BPD showed a pattern of greater decrease from pre-to post-treatment in amygdala activity for all three pictures types, but particularly in the left hemisphere and during the repeated emotional picture conditions (unpleasant and pleasant). None of the other interactions with Group reached statistical significance.



### 3.3. Self-report ratings of picture valence

Neither the Group  $\times$  Time  $\times$  Picture Type interaction, nor any interaction with Diagnostic group was significant for the SAM self-report ratings of picture valence. Both groups showed the standard, linear, stepwise self-report rating pattern of pleasant pictures being the most unpleasant, pleasant being the least unpleasant, and neutral being intermediate. The valence ratings for the HC group did not change over time (i.e. 0- vs. -12 months). However, it is noteworthy that compared with the HC group, the BPD group showed a trend for rating the unpleasant pictures as less unpleasant following DBT ( $p < 0.06$ ). We followed this finding up with a paired  $t$ -test for the BPD group comparing ratings for unpleasant pictures pre- and post-DBT which indicated that the patients rated the unpleasant pictures as less unpleasant post-DBT (pre-DBT:  $7.99 \pm 0.52$  post-DBT:  $7.42 \pm 0.62$ ,  $t(9) = 2.90$ ,  $p < 0.02$ ). Compared with HCs, there was a trend for the BPD group to rate the pleasant pictures as less pleasant at both the baseline and post-DBT time points (HC- vs. -BPD,  $p < 0.07$ ).

### 3.4. Amygdala and clinical change with DBT

Among the BPD patients, reduction in amygdala activity to repeated unpleasant pictures following DBT was associated with improved emotion regulation as measured by the change in total DERS score and the DERS Strategy subscale score ( $r = 0.70$ ,  $p < 0.02$ ,  $r = 0.69$ ,  $p < 0.02$ , respectively; Fig. 5).

## 4. Discussion

This is the *first* study to examine pre-post changes in amygdala activity with standard 1-year DBT treatment for BPD. The main findings are: a) BPD patients showed a reduction in overall amygdala activation following 12 months of DBT treatment ( $\eta^2 = 0.24$ ); b) this reduced amygdala activation in BPD patients post treatment was present in all three pictures types, but particularly notable in the left hemisphere and during the repeated emotional picture conditions ( $\eta^2 = 0.16$ ); c) among the BPD group, improvement in emotion regulation and strategy as measured by the DERS was associated with decreased amygdala activity to repeated unpleasant pictures ( $r = 0.70$ ,  $r = 0.69$ , respectively).

Strengths of our study include the use of: HC participants to capture longitudinal scanning effects of our paradigm, unmedicated, rigorously diagnosed patients with BPD without current MDD or bipolar disorder, a validated fMRI task of emotional processing, and DBT adherence ratings during delivery of the 1-year treatment.

Our findings are consistent with the only previous fMRI study of DBT (Schnell and Herpertz, 2007), which also found normalization of amygdala hyper-responsivity with successful DBT treatment in a 3-month pilot study. Our results build on these findings with a HC comparison group and empirically validated 1-year outpatient DBT treatment course with adherence ratings. In addition, our emotional task was selected for its emphasis on amygdala hyper-activity and habituation deficits in BPD.

Early models of emotional dysregulation in BPD include Siever and Davis (1991), and Linehan (1993) and a neuroimaging-based conceptualization describing a “hyperarousal-dyscontrol” syndrome (Lieb et al., 2004a). This syndrome is primarily characterized by

dysfunction in anterior regulatory regions including ACC and PFC, coupled with limbic structure hyper-reactivity, notably in amygdala and insula and supported by the findings of Silbersweig et al. (2007) and echoed in other populations of emotionally-dysregulated individuals including adolescents (Hare et al., 2008). A recent meta-analysis of neural correlates of negative emotionality in BPD (Ruocco et al., 2013) concluded that there is increased activation in the posterior cingulate and insula but *diminished activation* in a network extending from the amygdala to prefrontal regulatory regions including dorsolateral and subgenual PFC. Our results conflict with these findings but could be attributed to differences in study design, use of ROI methodology, patient selection including Axis I co-morbidity, hospitalization and/or medication status. For example, the studies reporting amygdala hyperactivity (e.g., Koenigsberg et al., 2009; Minzenberg et al., 2007; Schulze et al., 2011) involved unmedicated BPD patients, while the studies demonstrating diminished amygdala responsivity included participants currently taking psychotropic medications (Smoski et al., 2011). Similarly, Axis I co-morbidities such as PTSD may influence amygdala reactivity, particularly in relation to pain perception (Kraus et al., 2009). Cullen et al. (2011) reported increased amygdala connectivity during fear states in 12 females with BPD, suggesting increased use of both overt and automatic fear processing; however, the neutral state revealed lower connectivity between both bilateral amygdala and mid-cingulate regions. This inconsistency may stem, too, from differences in the type of stimuli employed and their personal relevance to the individual. Given research (e.g., Hazlett et al., 2007; Limberg et al., 2011) showing the importance of using BPD-salient stimuli (e.g., with abandonment, rejection themes) to elicit HC-BPD differences in affective startle modulation—a defensive response linked to amygdala activation, we chose IAPS pictures that had an interpersonal-social focus which may be of particular importance for delineating HC-BPD differences.

The finding of 12-month DBT treatment normalizing amygdala hyperactivity overlaps with findings of other psychotherapies for affective disorders. Treatment response to long-term psychodynamic psychotherapy has been found to correlate with decreases in anterior hippocampus/amygdala activity along with subgenual and medial PFC in MDD (Buchheim et al., 2012). Cognitive behavioral therapy treatment response is predicted by reduced medial pre-frontal activity and increased amygdala activation (Siegle et al., 2006). In MDD, pharmacologic interventions also target normalization of amygdala function (Sheline et al., 2001). While all our participants were free of current MDD, the role of amygdala hyperactivity in several affective disorders raises questions as to its specificity to BPD and as to the uniqueness of DBT vs. other forms of psychotherapy.

#### 4.1. Study limitations

Limitations of the study include the pilot nature of our study, low power and a small sample size. While this limitation renders our findings preliminary, significant between-group differences emerged, suggesting that further research and replication in this area is warranted. Given our small sample, we focused on the amygdala with an *a priori* hypothesis based upon our prior work showing habituation abnormalities in a larger sample ( $n = 33$ ) of unmedicated BPD patients compared with HCs, using an identical fMRI task and amygdala-centric focus (Hazlett et al., 2012).

The small size precludes differentiation of the sample based on treatment responders and nonresponders. Future work with a larger sample size will benefit from examining neurobiological parameters of treatment response, as has been argued by others (Schnell and Herpertz, 2007). In addition, our small sample size likely enhanced the magnitude of the correlation between the change in amygdala activity with treatment and DERS strategy and total scores (see Fig. 4). This limitation was discussed by Yarkoni (2009) and Vul et al. (2009) and highlights the potential for an exaggerated magnitude of correlations found in fMRI studies of emotion, personality and social cognition.

Additionally, our emotional task was a “passive viewing task” which means that we did not examine “active” emotion regulation, per se which might be considered a study limitation by some. However, given our prior work indicating that BPD patients evince a mismatch between their psychophysiological and self-report measures of emotion/valence (Hazlett et al., 2007, 2012), it could be argued that asking BPD participants whether they successfully regulated their emotions (i.e. using self-report) during a task involves a participant bias or demand characteristic which is a confound. Nevertheless, additional research is needed given recent research showing skill acquisition is critical to DBT treatment efficacy. This line of work will help us better understand the neurobiological changes that accompany amygdala quieting with successful psychotherapy.

It may also be argued that the community sample of subjects in this study were not fully representative of the larger pool of patients with BPD, limiting the generalizability of the findings. They were required to remain off all psychoactive medications during the duration of the 12-month DBT trial and pre/post fMRI imaging. Perhaps, this selected for a more cooperative, less symptomatic cohort. Lastly, without a comparison treatment condition, we cannot rule out the possibility that the amygdala changes observed in BPD were not due to other life events common to patients with BPD, but not controls.

#### 4.2. Future directions

Our investigation of the amygdala before and after 12-months of DBT treatment in BPD highlights the role of DBT treatment in quieting amygdala activity and the importance of enhancing emotional regulation strategies. Since our subjects were not treated with any psychiatric medication, these amygdala effects result from the psychotherapy intervention and suggest that patients are learning an adaptive process that counters emotionally-relevant activation of the amygdala. Future studies will benefit from parsing out which emotion regulation skills and strategies are necessary for a particular patient and how they combine for therapeutic and neurobiological effect.

Additional work with a larger BPD sample allowing for whole-brain analyses involving functional connectivity of the amygdala with other regions including prefrontal and anterior cingulate cortex is necessary to clarify how DBT-induced amygdala changes interact with other brain regions implicated in emotion regulation (Ochsner et al., 2002; Etkin et al., 2011). Future research similar to our study, examining the effects of evidence-based psychotherapy on underlying psychopathological mechanisms is critical to advance our understanding of the neuropathology of BPD, emotion regulation processes, and development of new treatment targets.

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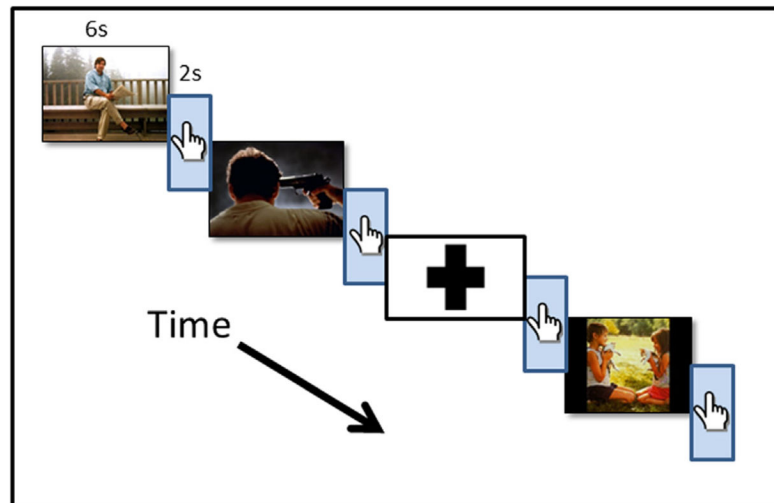
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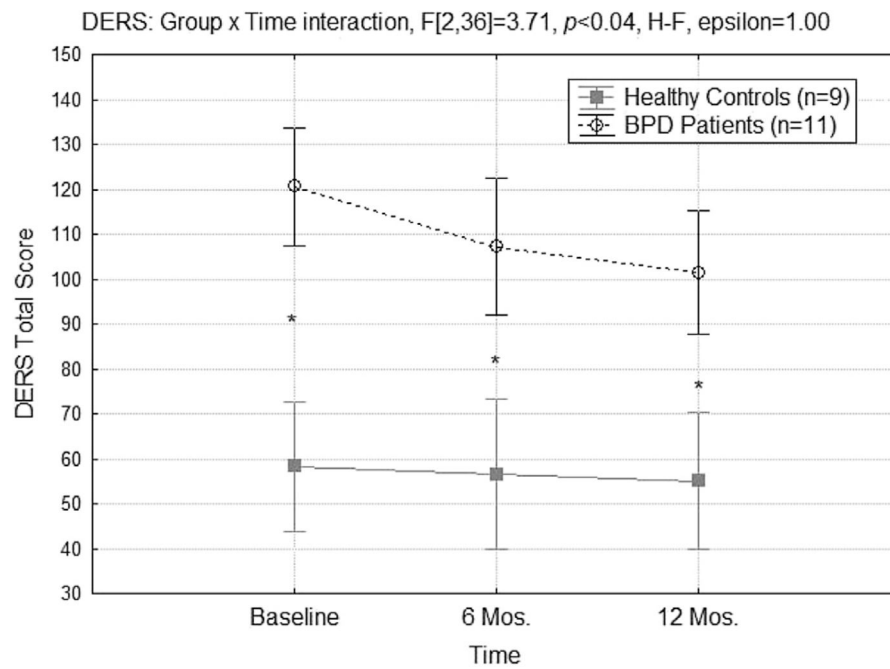


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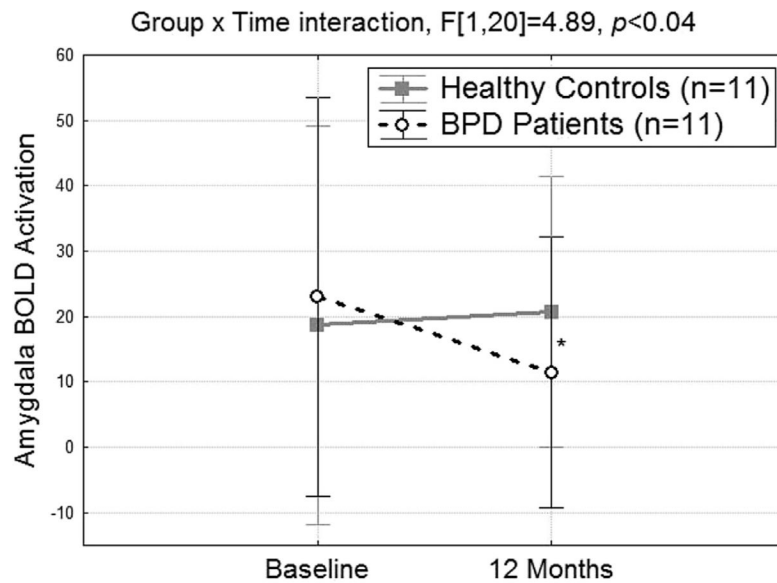
**Fig. 1.**

A schematic of the event-related picture processing fMRI task paradigm is shown. Participants viewed an intermixed series of unpleasant, neutral, and pleasant pictures for 6-s each. Following each picture, they were prompted with a screen to make a 3-choice button press to rate how the picture made them feel (unpleasant, neutral, or pleasant). Some trials had no picture presented during the 6-s period (see Methods section for additional details).



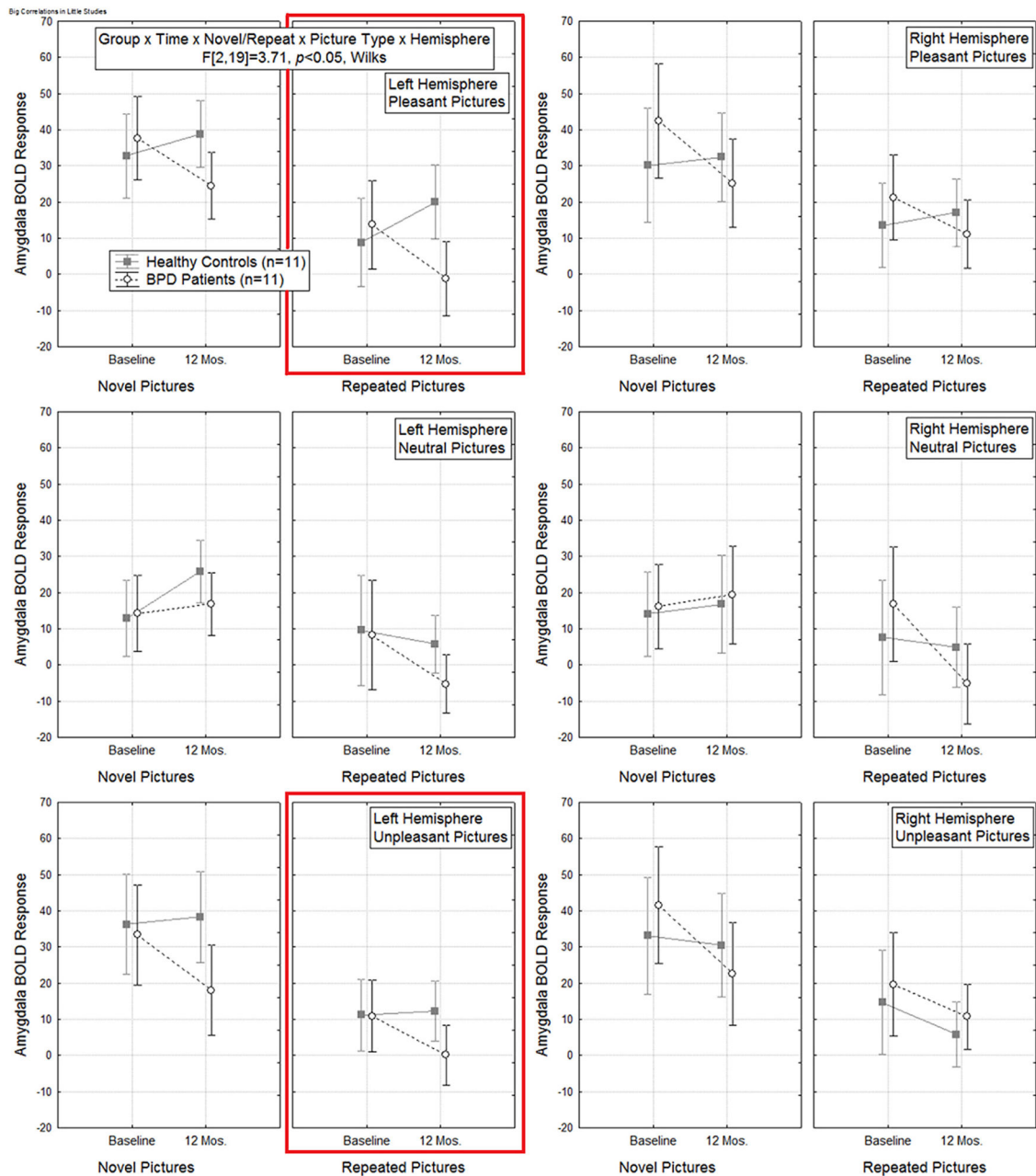
**Fig. 2.**

DERS total scores for the HC and BPD groups at baseline (0), 6 months, and 12 months. DERS scores showed a decline with DBT treatment in the BPD group, but were stable over time for the HC group, Group  $\times$  Time interaction,  $F[2,36] = 3.71$ ,  $p < 0.04$ , H-F, epsilon = 1.00.

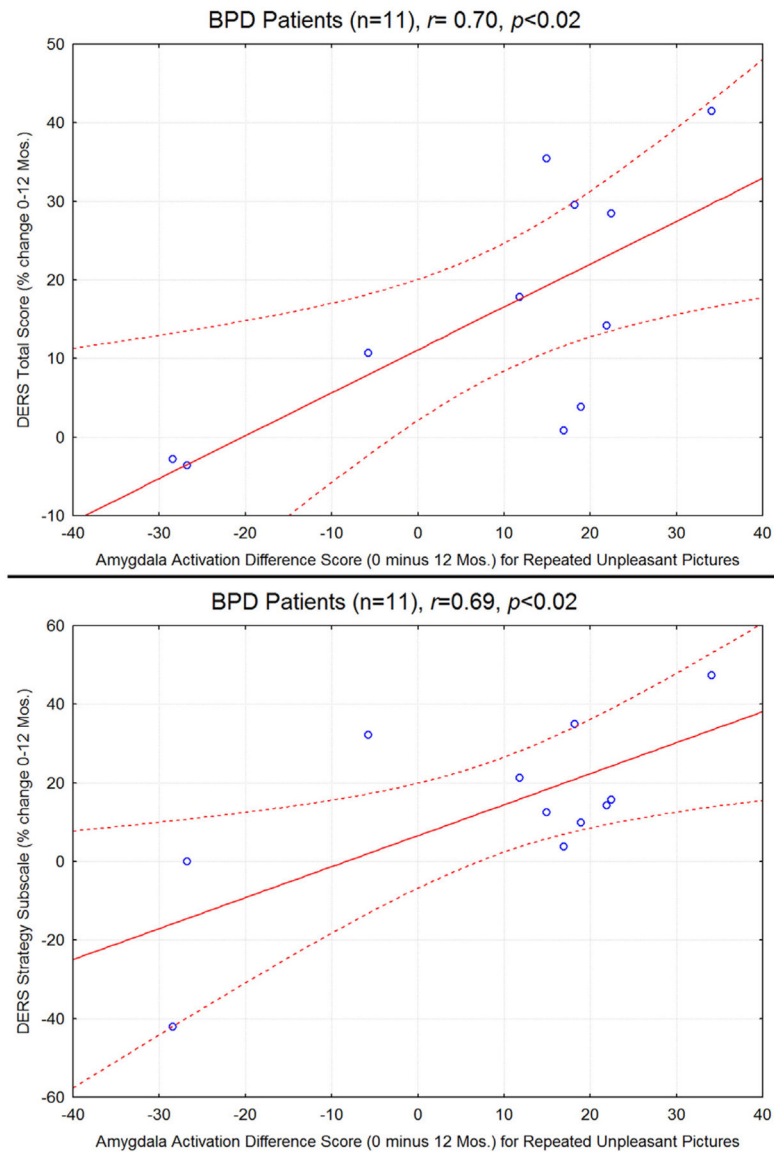


**Fig. 3.**

Compared with the healthy control (HC) group (which was yoked and did not receive treatment), the BPD group showed a pattern of higher amygdala activity at baseline (pre-treatment) that decreased following a standard 12-month DBT intervention. The HC group was scanned to provide a benchmark for normal amygdala activity at baseline and a 12-month interval. \* $p = 0.08$ , Fisher's LSD post-hoc, trend-level.

**Fig. 4.**

Compared with healthy controls, the individuals with BPD showed a pattern of greater decrease from pre- to post-treatment in amygdala activity for all three pictures types, but particularly in the left hemisphere and during the repeated emotional (unpleasant, pleasant) picture conditions (see red boxes in figure), Group  $\times$  Time  $\times$  Picture type  $\times$  Picture repetition  $\times$  Hemisphere interaction,  $F[2,19] = 3.71, p < 0.05$ . None of the post-hoc tests were significant. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Fig. 5.**

Scatterplots and Pearson correlation coefficients for the BPD group show the relationship between change (pre-treatment minus post-treatment, i.e. 0–12 months) in amygdala activation to repeated unpleasant pictures and emotional regulation (measured by change in the DERS total score (Top) and the DERS strategy subscale (Bottom)). Among the patient group, greater reduction in amygdala activity to repeated-unpleasant pictures (i.e. better habituation) following DBT was associated with greater clinical improvement in emotional regulation and use of emotion regulation strategies.



**Table 1**  
Demographic/Clinical Descriptors for Borderline Personality Disorder (BPD) and Healthy Control (HC) groups.

Characteristic	HC ( <i>n</i> = 11)		BPD ( <i>n</i> = 11)	
	<i>N</i>	%	<i>N</i>	%
Sex				
Female	9	81.8	9	81.8
Male	2	18.2	2	18.2
Psychiatric comorbidity				
Mood disorder (present)	0	0	0	0
Mood disorder (past)	0	0	8	72.7
PTSD (present)	0	0	1	9.1
Other anxiety disorder (present)	0	0	6	54.5
Substance use disorder (present)	0	0	0	0
Substance use disorder (past)	0	0	2	18.2
Psychosis	0	0	0	0

	Baseline		12-Month Follow-Up		Baseline		12-Month Follow-Up	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	30.4	10.4			32.8	11.5		
Education <sup>a</sup>	7.2	0.4			6.7	1.4		
DERS								
Total	56.6	14.9	54.8	14.4	120.5**	24.2	101.5**	25.7
Nonacceptance	8.7	2.9	9.0	3.4	20.5***	6.5	17.2**	7.1
Goals	9.2	4.4	8.7	3.9	20.9**	4.2	18.0**	5.0
Impulsivity	7.2	2.0	7.4	2.3	19.9**	5.1	15.1**	5.2
Awareness	13.2	4.7	12.0	4.8	17.7*	6.0	15.3	6.2
Strategies	11.2	4.2	11.2	3.9	26.2***	6.3	22.5**	6.2
Clarity	7.1	1.1	6.5	1.4	15.4**	4.7	13.5**	3.9
ZAN	0.6	1.3	0.7	0.7	18.1**	5.2	9.4**	6.2
HAM-D	–	–	–	–	13.8	5.6	12.0**	6.0

	Baseline		12-Month Follow-Up		Baseline		12-Month Follow-Up	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PANAS								
Positive Affect	38.3	5.1	39.7	5.0	23.1**	6.5	26.5**	8.7
Negative Affect	14.2	4.1	14.8	3.6	30.0**	10.9	27.1**	10.4

\*\*  $p < 0.004$ , BPD > HC,  $t$ -test.

\*  $p < 0.08$ , BPD > HC,  $t$ -test.

DERS = Difficulties in Emotion Regulation Scale, ZAN = Zanzarini Rating Scale for Borderline Personality Disorder, HAM-D = Hamilton Depression Rating Scale, and PANAS=Positive and Negative Affective Scale.

denotes significant change (0–12), paired  $t$ -test,  $p < 0.05$ .

Note: One HC did not have DERS, ZAN, or PANAS data, two HCs did not have education data.

<sup>a</sup> Education = highest degree earned: 1 = no high school diploma; 2 = GED; 3 = high school diploma; 4 = technical training; 5 = some college, no degree; 6 = Associate’s degree; 7 = Bachelor’s degree; 8 = Master’s degree; 9 = MD/PhD/JD/PharmD.