Journal of Psychiatric Research 57 (2014) 108–116

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

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

Marianne Goodman [a, b, d, *], David Carpenter [c], Cheuk Y. Tang [c], Kim E. Goldstein [a], Jennifer Avedon [b], Nicolas Fernandez [b], Kathryn A. Mascitelli [b], Nicholas J. Blair [b], Antonia S. New [a, b], Joseph Triebwasser [a, d], Larry J. Siever [a, b, d], Erin A. Hazlett [a, b]

[a] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[b] VISN 3 Mental Illness Research, Education, and Clinical Center (MIRECC), James J. Peters VA Medical Center, Bronx, NY, USA
[c] Department of Radiology, Icahn School of Medicine at Mount Sinai, USA
[d] Oupatient Psychiatry, James J. Peters VA Medical Center, Bronx, NY, USA

ARTICLE INFO

*Article history:*
Received 29 January 2014
Received in revised form
20 June 2014
Accepted 24 June 2014

*Keywords:*
Borderline personality disorder
Emotion regulation
Amygdala
Habituation
fMRI

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.
*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 × 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.

Published by Elsevier Ltd.

## 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

* Corresponding author. MIRECC, Room 6A-44, James J. Peters VA Medical Center, Bronx, NY 10468, USA. Tel.: +1 718 584 9000x5188; fax: +1 718 364 3576.
*E-mail addresses:* marianne.goodman@va.gov, mggoodman2001@yahoo.com (M. Goodman).

http://dx.doi.org/10.1016/j.jpsychires.2014.06.020
0022-3956/Published by Elsevier Ltd.

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 frontolimbic 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).

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

| Characteristic | HC ($n = 11$) | | BPD ($n = 11$) | |
|---|---|---|---|---|
| | *N* | % | *N* | % |
| 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[a] | 7.2 | 0.4 | | | 6.7 | 1.4 | | |
| DERS | | | | | | | | |
| Total | 56.6 | 14.9 | 54.8 | 14.4 | 120.5** | 24.2 | 101.5**Δ | 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**Δ | 5.0 |
| Impulsivity | 7.2 | 2.0 | 7.4 | 2.3 | 19.9** | 5.1 | 15.1**Δ | 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**Δ | 6.2 |
| Clarity | 7.1 | 1.1 | 6.5 | 1.4 | 15.4** | 4.7 | 13.5**Δ | 3.9 |
| ZAN | 0.6 | 1.3 | 0.7 | 0.7 | 18.1** | 5.2 | 9.4**Δ | 6.2 |
| HAM-D | – | – | – | – | 13.8 | 5.6 | 12.0** | 6.0 |
| 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**Δ | 10.4 |

**$p < 0.004$, BPD > HC, *t*-test.
*$p < 0.08$, BPD > HC, *t*-test.
DERS = Difficulties in Emotion Regulation Scale, ZAN = Zanarini Rating Scale for Borderline Personality Disorder, HAM-D = Hamilton Depression Rating Scale, and PANAS=Positive and Negative Affective Scale.
Δ 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.
[a] 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.

### 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)

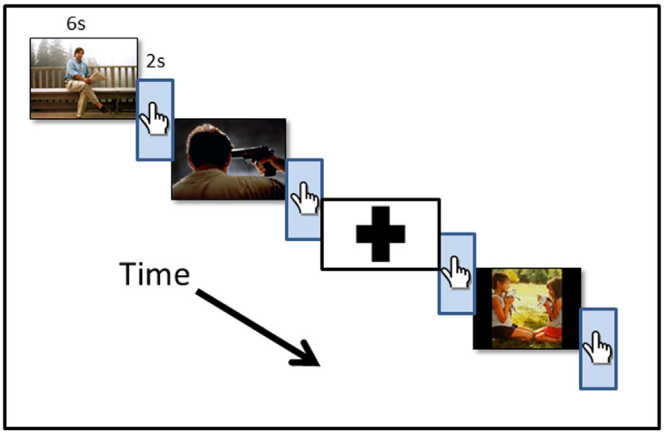


**Fig. 1.** A schematic of the event-related picture processing fMRI task paradigm is shown. Participants viewed an intermixed series of unpleasant, neutral, and pleasant pictures for 6-s each. Following each picture, they were prompted with a screen to make a 3-choice button press to rate how the picture made them feel (unpleasant, neutral, or pleasant). Some trials had no picture presented during the 6-s period (see Methods section for additional details).

(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*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 × 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°,FOV = 210 mm, matrix = 64 × 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 × 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

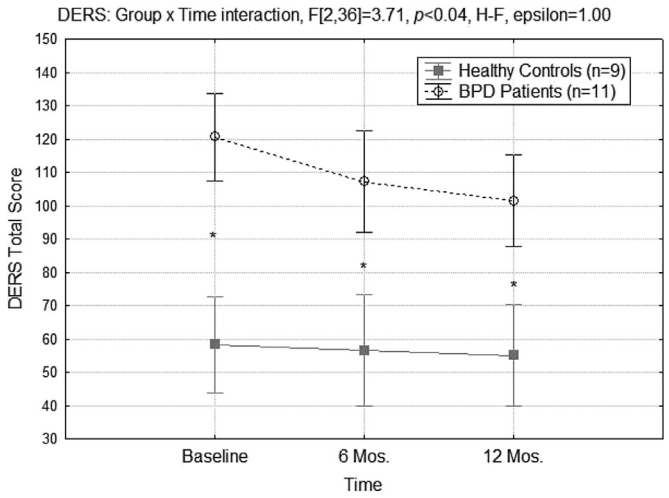


**Fig. 2.** DERS total scores for the HC and BPD groups at baseline (0), 6 months, and 12 months. DERS scores showed a decline with DBT treatment in the BPD group, but were stable over time for the HC group, Group × Time interaction, $F[2,36] = 3.71$, $p < 0.04$, H–F, epsilon = 1.00.

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 × 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 resulted indicated that the HC group did not show a

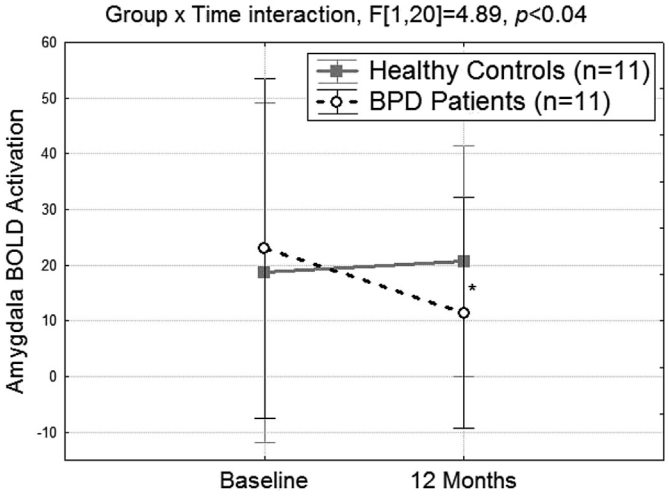


**Fig. 3.** Compared with the healthy control (HC) group (which was yoked and did not receive treatment), the BPD group showed a pattern of higher amygdala activity at baseline (pre-treatment) that decreased following a standard 12-month DBT intervention. The HC group was scanned to provide a benchmark for normal amygdala activity at baseline and a 12-month interval. *$p = 0.08$, Fisher's LSD post-hoc, trend-level.

significant change in amygdala activity over time, whereas the BPD group did (0–12 month difference scores: HC: 1.99 ± 16.67 (vs. 0, $p = 0.70$) vs. BPD:-11.54 ± 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 × Time × Picture type × Picture repetition × 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 × Time × 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 ± 0.52 post-DBT: 7.42 ± 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

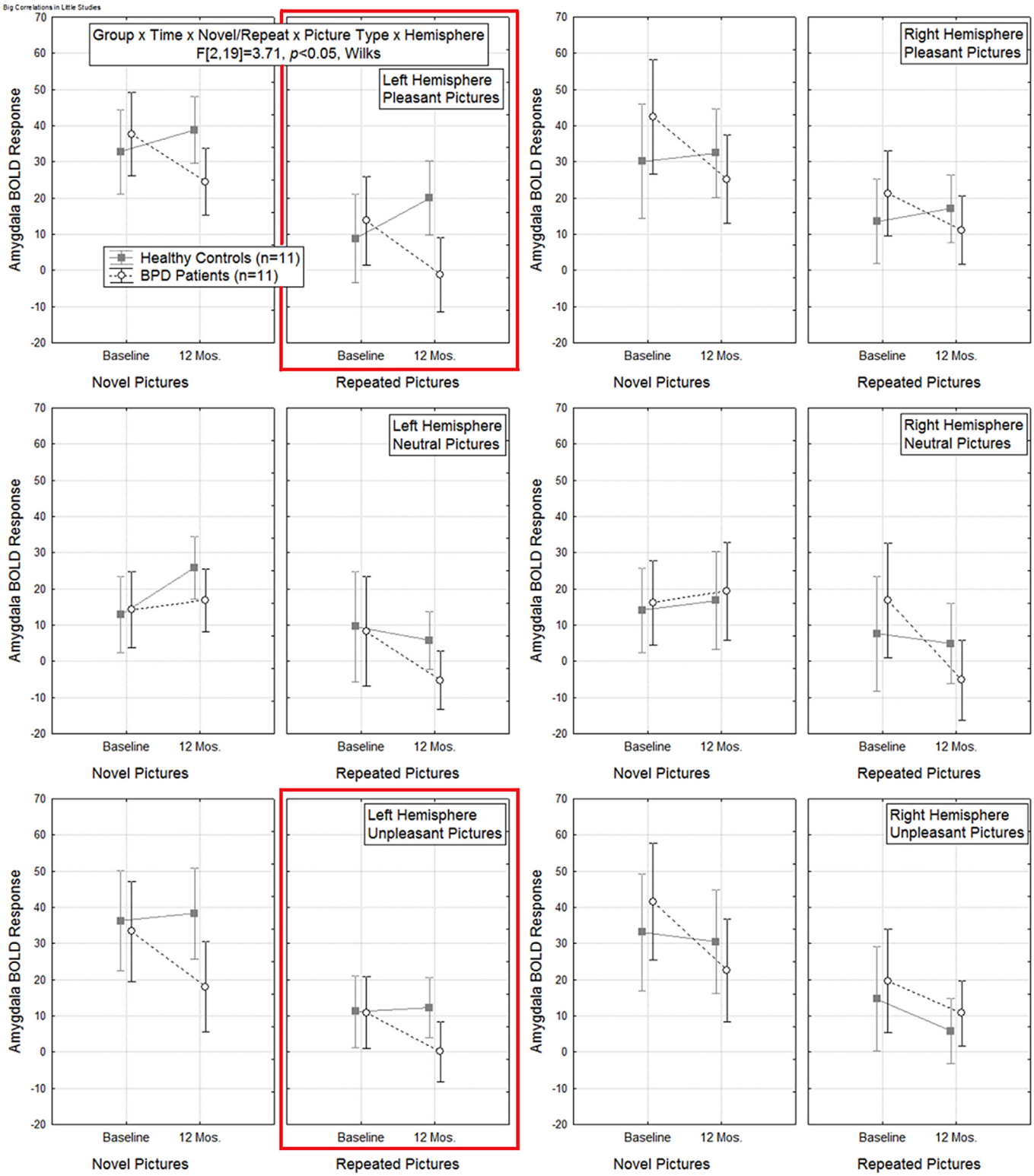


**Fig. 4.** Compared with healthy controls, the individuals with BPD showed a pattern of greater decrease from pre- to post-treatment in amygdala activity for all three pictures types, but particularly in the left hemisphere and during the repeated emotional (unpleasant, pleasant) picture conditions (see red boxes in figure), Group × Time × Picture type × Picture repetition × 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.)

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 hyperactivity 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

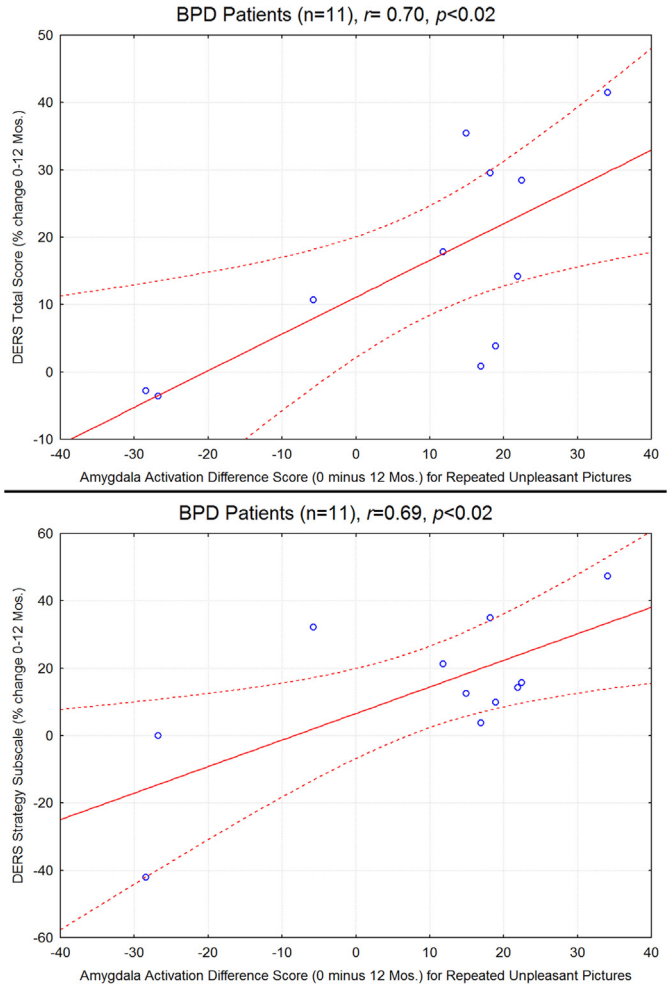


**Fig. 5.** Scatterplots and Pearson correlation coefficients for the BPD group show the relationship between change (pre-treatment minus post-treatment, i.e. 0–12 months) in amygdala activation to repeated unpleasant pictures and emotional regulation (measured by change in the DERS total score (Top) 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.

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 prefrontal 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.

## Role of the funding source

This research was supported by a Veterans' Administration Advanced Career Development Award (3277-06-109) to MG, NIMH Grant R01-MH073911 to EAH, Grant UL1TR000067 from the National Center for Advancing Translational Sciences, a component of the National Institutes of Health, and additional resources from the Mount Sinai GCRC, VISN 3 Mental Illness Research, Education and Clinical Center (MIRECC), James J. Peters Research Foundation.

## 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.

## Conflict of interest

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

## Acknowledgment

We acknowledge the DBT treatment provided by Drs. Lauren Helm, Gail Maurer and Lucia Vail, cooperation of the mental health clinical services of the James J. Peters VAMC.

## References

Arntz A, Appels C, Sieswerda S. Hypervigilance in borderline disorder: a test with the emotional Stroop paradigm. J Personal Disord 2000;14:366–73.
Beblo T, Driessen M, Mertens M, Wingenfeld K, Piefke M, Rullkoetter N, et al. Functional MRI correlates of the recall of unresolved life events in borderline personality disorder. Psychol Med 2006;36:845–56.
Bender DS, Dolan RT, Skodol AE, Sanislow CA, Dyck IR, McGlashan TH, et al. Treatment utilization by patients with personality disorders. Am J Psychiatry 2001;158:295–302.
Bohus M, Haaf B, Simms T, Limberger MF, Schmahl C, Unckel C, et al. Effectiveness of inpatient dialectical behavioral therapy for borderline personality disorder: a controlled trial. Behav Res Ther 2004;42:487–99.
Bradley MM, Lang PJ. Measuring emotion: the self-assessment manikin and the semantic differential. J Behav Ther Exp Psychiatry 1994;25:49–59.
Brody AL, Barsom MW, Bota RG, Saxena S. Prefrontal-subcortical and limbic circuit mediation of major depressive disorder. Semin Clin Neuropsychiatry 2001;6:102–12.
Buchheim A, Viviani R, Kessler H, Kachele H, Cierpka M, Roth G, et al. Changes in prefrontal-limbic function in major depression after 15 months of long-term psychotherapy. PLoS ONE 2012;7:e33745.
Carpenter RW, Trull TJ. Components of emotion dysregulation in borderline personality disorder: a review. Curr Psychiatry Rep 2013;15:335.
Cullen KR, Vizueta N, Thomas KM, Han GJ, Lim KO, Camchong J, et al. Amygdala functional connectivity in young women with borderline personality disorder. Brain Connect 2011;1:61–71.
Davidson RJ, Abercrombie H, Nitschke JB, Putnam K. Regional brain function, emotion and disorders of emotion. Curr Opin Neurobiol 1999;9:228–34.
de-Almeida CP, Wenzel A, De-Carvalho CS, Powell VB, Araujo-Neto C, Quarantini LC, et al. Amygdalar volume in borderline personality disorder with and without comorbid post-traumatic stress disorder: a meta-analysis. CNS Spectr 2012;17:70–5.
Donegan NH, Sanislow CA, Blumberg HP, Fulbright RK, Lacadie C, Skudlarski P, et al. Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. Biol Psychiatry 2003;54:1284–93.
Driessen M, Herrmann J, Stahl K, Zwaan M, Meier S, Hill A, et al. Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. Arch Gen Psychiatry 2000;57:1115–22.
Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci 2011;15:85–93.
First M, Gibbon M, Spitzer R. Structured clinical interview for DSM-IV Axis I Disorders (SCID-I). Washington, D.C.: American Psychiatric Publishing; 1996a.
First M, Gibbon M, Spitzer R. Structured clinical interview for DSM-IV Personality Disorders (SCIP-II). Washington, D.C.: American Psychiatric Publishing; 1996b.
Fossati A, Madeddu F, Maffei C. Borderline personality disorder and childhood sexual abuse: a meta-analytic study. J Personal Disord 1999;13:268–80.
Frankenburg FR, Zanarini MC. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. J Clin Psychiatry 2002;63:442–6.
Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, et al. Modulation of cortical-limbic pathways in major depression: treatment-specific

effects of cognitive behavior therapy. Arch Gen Psychiatry 2004;61:34–41.
Goldstein KE, Hazlett EA, New AS, Haznedar MM, Newmark RE, Zelmanova Y, et al. Smaller superior temporal gyrus volume specificity in schizotypal personality disorder. Schizophr Res 2009;112:14–23.
Goodman M, New A, Siever L. Trauma, genes, and the neurobiology of personality disorders. Ann N Y Acad Sci 2004;1032:104–16.
Gratz KL, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. J Psychopathol Behav Assess 2004;26:41–54.
Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatr 1960;23:56–62.
Hare T, Tottenham N, Galvan A, Voss H, Glover G, Casey BJ. Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. Biol Psychiatry 2008;63:927–34.
Hazlett EA, Speiser LJ, Goodman M, Roy M, Carrizal M, Wynn JK, et al. Exaggerated affect-modulated startle during unpleasant stimuli in borderline personality disorder. Biol Psychiatry 2007;62:250–5.
Hazlett EA, Zhang J, New AS, Zelmanova Y, Goldstein KE, Haznedar MM, et al. Potentiated amygdala response to repeated emotional pictures in borderline personality disorder. Biol Psychiatry 2012;72:448–56.
Herpertz SC, Kunert HJ, Schwenger UB, Sass H. Affective responsiveness in borderline personality disorder: a psychophysiological approach. Am J Psychiatry 1999;156:1550–6.
Herpertz SC, Dietrich TM, Wenning B, Krings T, Erberich SG, Willmes K, et al. Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. Biol Psychiatry 2001;50:292–8.
Herpertz SC, Koetting K. Startle response in inpatients with borderline personality disorder vs. healthy controls. J Neural Transm 2005;112:1097–106.
Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 2002;17:825–41.
Kleindienst N, Limberger MF, Ebner-Priemer UW, Keibel-Mauchnik J, Dyer A, Berger M, et al. Dissociation predicts poor response to dialectical behavioral therapy in femal patients with borderline personality disoder. J Personal Disord 2011;25:432–47.
Koenigsberg HW, Siever LJ, Lee H, Pizzarello S, New AS, Goodman M, et al. Neural correlates of emotion processing in borderline personality disorder. Psychiatry Res 2009;172:192–9.
Koenigsberg HW. Affective instability: toward an integration of neuroscience and psychological perspectives. J Personal Disord 2010;24:60–82.
Koenigsberg HW, Denny BT, Fan J, Liu X, Guerreri S, Mayson SJ, et al. The neural correlates of anomalous habituation to negative emotional pictures in borderline and avoidant personality disorder patients. Am J Psychiatry 2014;171:82–90.
Kraus A, Esposito F, Seifritz E, Di Salle F, Ruf M, Valerius G, et al. Amygdala deactivation as a neural correlate of pain processing in patients with borderline personality disorder and co-occurrent posttraumatic stress disorder. Biol Psychiatry 2009;65:819–22.
Lang P, Bradley MM. The International Affective Picture System (IAPS) in the study of emotion and attention. Handbook of emotion elicitation and assessment; 2007. p. 29.
Lieb K, Rexhausen JE, Kahl KG, Schweiger U, Philipsen A, Hellhammer DH, et al. Increased diurnal salivary cortisol in women with borderline personality disorder. J Psychiatr Res 2004a;38:559–65.
Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. Borderline personality disorder. Lancet 2004b;364:453–61.
Limberg A, Barnow S, Freyberger HJ, Hamm AO. Emotional vulnerability in borderline personality disorder is cue specific and modulated by traumatization. Biol Psychiatry 2011;69:574–82.
Linehan MM, Armstrong HE, Suarez A, Allmon D, Heard HL. Cognitive-behavioral treatment of chronically parasuicidal borderline patients. Arch Gen Psychiatry 1991;48:1060–4.
Linehan MM. Cognitive behavioral treatment of borderline personality disorder. New York: The Guilford Press; 1993.
Links PS, Heslegrave R, van Reekum R. Prospective follow-up study of borderline personality disorder: prognosis, prediction of outcome, and Axis II comorbidity. Can J Psychiatry 1998;43:265–70.
Links PS, Eynan R, Heisel MJ, Nisenbaum R. Elements of affective instability associated with suicidal behaviour in patients with borderline personality disorder. Can J Psychiatry 2008;53:112–6.
Lis E, Greenfield B, Henry M, Guile JM, Dougherty G. Neuroimaging and genetics of borderline personality disorder: a review. J Psychiatry Neurosci 2007;32:162–73.
Marwaha S, He Z, Broome M, Singh SP, Scott J, Eyden J, et al. How is affective instability defined and measured? A systematic review. Psychol Med 2013:1–16.
Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. Br Med Bull 2003;65:193–207.
Minzenberg MJ, Fan J, New AS, Tang CY, Siever LJ. Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study. Psychiatry Res 2007;155:231–43.
New AS, Hazlett EA, Buchsbaum MS, Goodman M, Mitelman SA, Newmark R, et al. Amygdala-prefrontal disconnection in borderline personality disorder. Neuropsychopharmacology 2007;32:1629–40.
Neacsiu AD, Rizvi SL, Linehan MM. Dialectical behavior therapy skills use as a mediator and outcome of treatment for borderline personality disorder. Behav Res Ther 2010; Sep;48(9):832–9. Epub 2010 May 23.
Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking Feelings: an fMRI study of cognitive regulation of emotion. J Cogn Neurosci 2002;14:1215–29.
Renaud SM, Zacchia C. Toward a definition of affective instability. Harv Rev Psychiatry 2012;20:298–308.
Ruocco AC, Amirthavasagam S, Choi-Kain LW, McMain SF. Neural correlates of negative emotionality in borderline personality disorder: an activation-likelihood-estimation meta-analysis. Biol Psychiatry 2013;73:153–60.
Rusch N, van Elst LT, Ludaescher P, Wilke M, Huppertz HJ, Thiel T, et al. A voxel-based morphometric MRI study in female patients with borderline personality disorder. Neuroimage 2003;20:385–92.
Schmahl C, Bohus M, Esposito F, Treede RD, Di Salle F, Greffrath W, et al. Neural correlates of antinociception in borderline personality disorder. Arch Gen Psychiatry 2006;63:659–67.
Schneider W, Eschmann A, Zuccolotto A. E-Prime user's guide. Pittsburgh, PA: Psychology Software Tools, Inc.; 2002.
Schnell K, Herpertz SC. Effects of dialectic-behavioral-therapy on the neural correlates of affective hyperarousal in borderline personality disorder. J Psychiatr Res 2007;41:837–47.
Schulze L, Domes G, Kruger A, Berger C, Fleischer M, Prehn K, et al. Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. Biol Psychiatry 2011;69:564–73.
Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry 2001;50:651–8.
Siegle GJ, Carter CS, Thase ME. Use of FMRI to predict recovery from unipolar depression with cognitive behavior therapy. Am J Psychiatry 2006;163:735–8.
Siever LJ, Davis KL. A psychobiological perspective on the personality disorders. Am J Psychiatry 1991;148:1647–58.
Silbersweig D, Clarkin J, Goldstein M, Kernberg O, Tuescher O, Levy K, et al. Failure of frontolimbic inhibitory function in the context of negative emotion in borderline personality disorder. Am J Psychiatry 2007;164:1832–41.
Skodol AE, Siever LJ, Livesley WJ, Gunderson JG, Pfohl B, Widiger TA. The borderline diagnosis II: biology, genetics, and clinical course. Biol Psychiatry 2002;51:951–63.
Smith SM. Fast robust automated brain extraction. Hum Brain Mapp 2002;17:143–55.
Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23:S208–19.
Smoski MJ, Salsman N, Wang L, Smith V, Lynch TR, Dager SR, et al. Functional imaging of emotion reactivity in opiate-dependent borderline personality disorder. Personal Disord 2011;2:230–41.
StatSoft Inc. Statistica, Version 9.1; 2010. Tulsa, OK, www.statsoft.com.
Tebartz van Elst L, Hesslinger B, Thiel T, Geiger E, Haegele K, Lemieux L, et al. Frontolimbic brain abnormalities in patients with borderline personality disorder: a volumetric magnetic resonance imaging study. Biol Psychiatry 2003;54:163–71.
Vul E, Harris C, Winkielman P, Pashler H. Puzzingly high correlations in fMRI studies of emotion, personality, and social cognition. Perspect Psychol Sci 2009;4:274–90.
Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54:1063–70.
Wingenfeld K, Rullkoetter N, Mensebach C, Beblo T, Mertens M, Kreisel S, et al. Neural correlates of the individual emotional Stroop in borderline personality disorder. Psychoneuroendocrinology 2009;34:571–86.
Yarkoni T. Big Correlations in little studies: Inflated fMRI Correlations Reflect Low Statistical Power – Commentary on Vul et al. (2009). Perspect Psychol Sci 2009;4:294–8.
Yen S, Zlotnick C, Costello E. Affect regulation in women with borderline personality disorder traits. J Nerv Ment Dis 2002;190:693–6.