Neural Correlates of Memories of Abandonment in Women with and without Borderline Personality Disorder

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Background: *Borderline personality disorder (BPD) is a common psychiatric disorder that is often linked to early stressors. One particularly salient feature of the disorder is fear of abandonment. This pilot study was conducted to measure neural correlates of memories of abandonment in women with and without BPD.*

Methods: *Twenty women with a history of childhood sexual abuse underwent measurement of brain blood flow with positron emission tomography imaging while they listened to scripts describing neutral and personal abandonment events. Brain blood flow during exposure to abandonment and neutral scripts was compared among women with and without BPD.*

Results: *Memories of abandonment were associated with greater increases in blood flow in bilateral dorsolateral prefrontal cortex (middle frontal gyrus, Brodmann's areas 9 and 10) as well as right cuneus (area 19) in women with BPD than in women without BPD. Abandonment memories were associated with greater decreases in right anterior cingulate (areas 24 and 32) in women with BPD than in women without BPD.*

Conclusions: *These findings implicate dysfunction of dorsolateral and medial prefrontal cortex including anterior cingulate, left temporal cortex, and visual association cortex in memories of abandonment in women with BPD. These brain areas may mediate symptoms of BPD.* Biol Psychiatry 2003;54:142–151 © *2003 Society of Biological Psychiatry*

Key Words: Borderline personality disorder, abandonment, early life stress, childhood abuse, cerebral blood flow

Introduction

Borderline personality disorder (BPD) is a highly prevalent condition affecting approximately 1.3% of the population (Torgersen et al 2001). Although a number of studies have looked at psychosocial factors related to the disorder, little is known about the biology of BPD. Among the most important psychosocial factors involved in the development of BPD are childhood sexual and physical abuse (Zanarini 1997). Recently, however, other adverse experiences including emotional abuse and neglect have become amenable to study. There is evidence that these experiences may be equally detrimental to outcome (Bremner et al 2000). Abandonment represents one example of a situation of emotional abuse, particularly salient for the case of BPD. It has been hypothesized that being left alone or "abandoned" are integral in the development of BPD, and certainly the fear of abandonment and intolerance of aloneness are an integral part of the clinical presentation of patients with BPD (Benjamin 1996; Gunderson 1996, 2001). The *Diagnostic and Statistical Manual of Mental Disorders* in fact includes "frantic efforts to avoid real or imagined abandonment" as one of the nine diagnostic criteria for BPD (American Psychiatric Association 2000).

Recently it has been suggested that BPD may be part of a stress-related psychiatric disorder spectrum (Bremner 2002). Animal studies using a variety of stressors including electric shock or social defeat showed damage to hippocampal neurons and inhibition of neurogenesis. The mechanisms of these effects may be related to stress-induced elevations in cortisol, decreased brain-derived neurotrophic factor (BDNF), elevations in glutamate, or other factors (reviewed in Bremner 2002). In humans, this stress-induced brain damage may lead to the development of a range of psychiatric disorders with a common relationship to stress, including depression, posttraumatic stress disorder (PTSD), dissociative disorders, and BPD. A trauma spectrum model would help to explain the high

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comorbidity for PTSD (50%) seen in BPD patients (McGlashan et al 2000).

The neural circuitry of stress and emotion may have applications for understanding the pathophysiology of BPD. Brain areas that mediate emotion and the response to threat also play a critical role in memory and visuospatial processing and are localized in prefrontal and limbic cortex areas (Bremner et al 1995). Prefrontal cortex can be divided into two anatomically and functionally distinct parts, medial and dorsolateral prefrontal cortex. Medial prefrontal cortex consists of several related areas, including orbitofrontal cortex, anterior cingulate (Brodmann's areas 25 and area 32), and anterior prefrontal cortex (Brodmann's areas 9 and 10). This area also has important inhibitory inputs to the amygdala that mediate extinction to fear response (Morgan and LeDoux 1995). Human subjects with lesions of the prefrontal cortex show dysfunction of normal emotions and an inability to relate in social situations that require correct interpretation of the emotional expressions of others (Damasio et al 1994). These findings suggest that dysfunction of medial prefrontal cortex may play a role in pathologic emotions that sometimes follow exposure to stressors as seen in BPD. Dorsolateral prefrontal cortex has been assigned a major role in short-term or working memory but also participates in aspects of emotional processing (Davidson et al 2000).

Other brain areas that are interconnected with prefrontal cortex play an important role in the stress response. The amygdala plays a central role in conditioned fear responses (Davis 2001; LeDoux 1993). The declarative memory functions of the hippocampus are important in accurately identifying the signal of potential threat during stress situations. The hippocampus is also involved in fear responses to the context of a stressful situation (Kim and Fanselow 1992; Phillips and LeDoux 1992). Stress results in damage to hippocampal neurons with associated deficits in memory (McEwen and Magarinos 2001; Sapolsky 1996).

Neuroimaging studies in another stress-related disorder, PTSD following childhood abuse, have demonstrated abnormalities in brain areas involved in memory. Shin et al (1999) investigated 16 women with childhood abuse (8 women with PTSD and 8 women without PTSD) with positron emission tomography (PET) while they listened to personalized scripts of traumatic events. Both groups exhibited regional cerebral blood flow increases in orbitofrontal cortex and anterior temporal poles during the traumatic script compared with a neutral script; these increases were greater in the PTSD group. The PTSD group showed greater decreases in anterior frontal cortex areas (areas 9 and 10) than the comparison group. In a second PET study of abuse-related memories in 22 women with a history of childhood sexual abuse (10 with and 12 without PTSD) (Bremner et al 1999a), the PTSD group revealed greater increases in blood flow in the dorsolateral prefrontal cortex (areas 6 and 9), posterior cingulate (area 31), and motor cortex, as well as a failure of activation in anterior cingulate (area 32). There was also decreased blood flow in right hippocampus, fusiform/inferior temporal gyrus, supramarginal gyrus, and visual association cortex in women with PTSD relative to women without PTSD.

Functional neuroimaging studies of BPD patients have been limited. De la Fuente et al (1997) used 18-fluorodeoxyglucose (FDG) PET for baseline measures of cerebral glucose metabolism. They found decreased metabolism in premotor and prefrontal areas; the anterior part of the cingulate cortex; and the thalamic, caudate, and lenticular nuclei in BPD patients compared with control subjects. In a pilot study of five BPD patients and eight control subjects, Soloff (2000) found greater FDG uptake in response to the serotonergic agonist fenfluramine in medial and orbital regions of right prefrontal cortex (area 10), left middle and superior temporal gyri, left parietal lobe, and left caudate body in control participants compared with patients. There were no areas in which patients had greater relative regional uptake than control subjects.

No studies have used activation of symptoms of BPD in conjunction with PET to measure neural correlates of BPD. The purpose of this pilot study was to use PET in the examination of neural correlates of memories of abandonment in patients with BPD. Based on the findings just described for abuse-related PTSD, we hypothesized that exposure to scripts of abandonment situations would result in decreased blood flow in medial prefrontal cortex, fusiform gyrus, and visual association cortex and in increased activation in dorsolateral prefrontal cortex in women with BPD relative to control subjects.

Methods and Materials

Subjects

The study was approved by the Human Investigation Committee of Yale University, as well as the Human Studies Subcommittee of the VA Connecticut Healthcare System. Twenty women with a history of sexual or physical abuse participated in the study. Subjects included women with (n = 10) and without (n = 10) BPD. All subjects were recruited through newspaper and flyer advertisement. Axis I diagnoses were assessed by a trained psychiatrist and psychologist (CGS and BME) using the Structured Clinical Interview for DSM-IV Axis I disorders (Spitzer et al 1995). Axis II diagnoses were assessed using the Diagnostic Interview for Personality Disorders (Zanarini et al 1996). All subjects gave written informed consent for participation, were free of major medical illness on the basis of history and physical examination and laboratory testing, and were not actively abusing substances or alcohol (in the past 3 months). Eight of the control participants were free of psychotropic medication; 8 of

Table 1. Comorbid Psychiatric Disorders and Psychotropic Medication for All Participants

	SCID Current Diagnoses	SCID Lifetime[a] Diagnoses	Psychotropic Medication
Control			
1	Panic disorder with agoraphobia	MDD, cannabis dependence, panic disorder with agoraphobia	None
2	None	MDD, anorexia nervosa, bulimia nervosa	None
3	None	None	None
4	None	MDD	None
5	None	MDD, alcohol dependence, polysubstance dependence, bulimia nervosa	Sertraline, Risperidone, Disulfiram, Bupropion
6	None	PTSD, MDD	None
7	None	None	None
8	None	None	None
9	Social phobia	PTSD, social phobia, panic disorder without agoraphobia	None
10	None	PTSD	Paroxetine
BPD Subjects			
1	PTSD, MDD	PTSD, MDD	Citalopram
2	None	Cannabis dependence, opioid dependence	Paroxetine, Olanzapine
3	PTSD, MDD, panic disorder with agoraphobia	PTSD, MDD, panic disorder with agoraphobia	Paroxetine, Divalproex Sodium, Chlorpromazine
4	Dysthymic disorder, generalized anxiety disorder, panic disorder without agoraphobia, bulimia nervosa	PTSD, dysthymic disorder, generalized anxiety disorder, panic disorder without agoraphobia, bulimia nervosa	Paroxetine
5	PTSD, bipolar I disorder mixed episode, bulimia nervosa	PTSD, bipolar I disorder, bulimia nervosa, alcohol dependence, cocaine abuse	Bupropion, Divalproex Sodium
6	MDD, body dysmorphic disorder, bulimia nervosa	MDD, body dysmorphic disorder, bulimia nervosa, alcohol dependence	None
7	None	Bipolar I disorder, alcohol abuse, polysubstance dependence	Gabapentin, Olanzapine
8	PTSD, panic disorder with agoraphobia, social phobia, obsessive compulsive disorder	PTSD, bipolar I disorder, panic disorder with agoraphobia, social phobia, obsessive compulsive disorder, alcohol dependence, cannabis dependence	None
9	PTSD, panic disorder with agoraphobia, dysthymic disorder, social phobia	PTSD, MDD, dysthymic disorder, panic disorder with agoraphobia, social phobia, Alcohol dependence, cocaine dependence	Quetiapine, Venlafaxine
10	Bipolar I disorder, depressed episode	Bipolar I disorder, amphetamine abuse	Bupropion, Divalproex Sodium

BPD, borderline personality disorder; MDD, major depressive disorder; PTSD, posttraumatic stress disorder; SCID, Structured Clinical Interview for DSM-IV.
[a]Past or current.

the 10 BPD subjects were on antidepressant or neuroleptic medication, two were medication free; no subject was taking benzodiazepine medication. Table 1 lists psychotropic medication as well as comorbid current and lifetime diagnoses of psychiatric disorders for all participants.

Subjects with a serious medical or neurologic illness, organic mental disorder or comorbid psychotic disorders, retained metal, a history of head trauma, loss of consciousness, cerebral infectious disease, or dyslexia were excluded. There were no major differences in age between the BPD (mean = 30 years) and the control subjects (mean = 33 years). All BPD participants and 9 of 10 control participants were right-handed.

History of childhood abuse was assessed with the self-report version of the Early Trauma Inventory (ETI). The ETI is an interview assessing physical, emotional, and sexual abuse, as well as general traumatic events. The clinician-administered version of the ETI has been demonstrated to be reliable and valid in the assessment of childhood trauma (Bremner et al 2000), and the self-report ETI has been validated against the clinician-administered ETI. Mean ETI score in the BPD group was 73.8; mean ETI score in the control group was 61.3 (*ns*).

Procedure

Each subject, with the assistance of the interviewer, prepared two personalized scripts of situations of abandonment, each 1 min in length, that were experienced as aversive by the subject. The two scripts described either two aspects of a single event or two different events. These scripts were later read aloud to the subject during the scanning session.

Each subject underwent four scans on a single day. The subject was placed in the scanner with her head in a holder to minimize motion and positioned with the canthomeatal line parallel to an external laser light. An intravenous line was inserted for administration of $[^{15}O]H_2O$. Following positioning within the camera gantry, a transmission scan of the head was obtained by using an external $^{67}Ga/^{68}Ge$ rod source, to correct emission data for attenuation due to overlying bone and soft tissue. Baseline

ratings were then collected, including the Clinician Administered Dissociative States Scale, a reliable and valid 27-item scale for the measurement of current dissociative states (Bremner et al 1998), the Borderline Personality Disorder Symptom Scale, a 10-item instrument for the assessment of borderline state symptoms (Schmahl et al, in preparation), the Subjective Units of Distress Scale (a visual analog scale scored from 0–100 for the assessment of current subjective level of distress), and two scales for the assessment of fear and anxiety scored from 0–4 (Southwick et al 1993).

Subjects then underwent scanning during readings of neutral and abandonment script. All scripts were 1 min in length and were read aloud in a normal tone of voice by a female research associate, who was blind to the diagnostic group. First, subjects underwent two scans while listening to two standardized neutral narratives (one about baking a birthday cake and the other about going shopping) preceded by instructions to listen carefully and form an image in their mind. The neutral narratives were standardized for all subjects and were not personalized to the subjects' individual experience. Then subjects underwent two scans, during which they listened to two personalized scripts of their own abandonment event; the scripts were again preceded by instructions to listen carefully and form an image in their mind. A fixed order (neutral scripts followed by abandonment scripts) was used for all subjects to prevent anxiety elicited by the abandonment scripts from persisting into the neutral scripts.

According to the logic of the study design, differences in brain blood flow between the abandonment scripts and the neutral scripts would be secondary to the specific effects of memories of abandonment, controlling for other factors, including attention, auditory perception, and comprehension of a coherent verbal narrative.

At the same time of the beginning of the reading of the script, subjects received a bolus of 30 mCi of $[^{15}O]H_2O$, followed 10 sec later by a PET scan acquisition that was 80 sec in length. The onset of the PET scan acquisition was timed to correspond to the point of maximum rate of increase in uptake of tracer into the brain. The script was timed to effect maximum levels of symptoms at the time of maximal uptake of tracer in the brain. With the bolus injection method of $[^{15}O]H_2O$ (which has a half-life of 110 sec), tracer peaks at 10 sec, with 90% of counts obtained in the first 60 sec after peak, which is the time during which the scripts were read. The PET imaging was performed with a Posicam PET camera (Positron Corp., Houston, TX; in plane resolution after filtering, 6-mm full width at half maximum, measured with a F-18 filled phantom). At the termination of the script presentation subjects were asked to rate symptoms using the Clinician Administered Dissociative States Scale, the Borderline Personality Disorder Symptom Scale, the Subjective Units of Distress Scale, and a visual analog scale for the assessment of fear and anxiety.

Image Analysis

Images were reconstructed and analyzed on a Sun Sparc workstation through use of statistical parametric mapping (SPM96; www.fil.ion.ucl.ac.uk/spm/spm96.html). Images for each patient set were realigned to the first scan of the study session. The mean concentration of radioactivity in each scan was obtained as an area-weighted sum of the concentration of each slice and was adjusted to a nominal value of 50 mL/min per 100 g. The data underwent transformation into a common anatomic space (SPM96 template) and were smoothed with a three-dimensional gaussian filter to 16-mm full width at half maximum. Regional blood flow, with global blood flow as a covariate, was compared between abandonment and neutral script conditions for the women with and without BPD. The interaction between group (BPD vs. non-BPD) and condition (abandonment vs. neutral scripts) was also examined. Statistical analyses yielded image data sets in which the values assigned to individual voxels correspond to the t statistics (Friston et al 1991). Statistical images were displayed with values of z score units. A threshold z score of 2.58 ($p < .005$, uncorrected for multiple comparisons) was used to examine areas of activation within hypothesized areas (medial prefrontal cortex, dorsolateral prefrontal cortex, visual association cortex, fusiform gyrus). A threshold z score of 2.58 has been demonstrated by Reiman et al (1997) to be associated with a low rate of false positive activations and to constitute the most optimal trade-off between type I and type II statistical errors. We also used a minimum cluster size of 30 voxels in an effort to control for type I errors. A z score of 2.33 ($p < .01$, uncorrected for multiple comparisons) was used for comparison of groups. Because our hypotheses were based on findings in abuse-related PTSD and because this is, to our knowledge, the first neuroimaging study of symptom provocation in BPD, we performed analyses of activation patterns on a whole brain basis for exploratory purposes to generate hypotheses for future studies in BPD. A fixed-effects analysis was employed in this analysis that will limit the ability to generalize from the study population. Location of areas of activation was identified as the distance from the anterior commisure in millimeters, with x, y, and z coordinates; a standard stereotaxic atlas was used to identify regions of activation (Talairach and Tournoux 1988).

Behaviorial measures (Borderline Personality Disorder Symptom Scale, Clinician Administered Dissociative States Scale, Subjective Units of Distress Scale, and analog rating scores) were compared for BPD and comparison subject groups through use of repeated-measures analysis of variance, with behavioral state over time (baseline and neutral and abandonment script periods) as the repeated measure.

Results

Psychological ratings revealed a significant time effect for all ratings and a significant diagnosis-by-time interaction for the Borderline Personality Disorder Symptom Scale (Table 2, Figure 1).

Deactivation in right precuneus (area 7) and right caudate with memories of abandonment was nonspecifically seen in women both with and without BPD. In the control group, we found several regions of activation as well as of deactivation in the cerebellum (Table 3). In the BPD group there was deactivation in the cerebellum to a greater degree than in the controls (Table 4).

Table 2. Psychological Ratings for Women with and without BPD after Listening to Two Neutral Scripts and Two Scripts Describing an Abandonment Situation

	Neutral Script						Abandonment Script			
	Baseline		1		2		1		2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Women with BPD (n = 10)										
BPD Symptom Scale (0–40)[a,b]	2.3	1.0	1.4	.6	4.2	1.2	9.0	2.0	11.1	2.3
Clinician Administered Dissociative States Scale (0–76)[a]	3.2	.7	3.0	.7	4.4	.7	7.0	1.3	7.1	1.6
Fear (analog scale, 0–4)[a]	.4	.2	.4	.2	.7	.3	.8	.2	.2	.1
Anxiety (analog scale, 0–4)[a]	1.1	.3	.8	.2	.9	.3	1.6	.3	1.7	.4
Subjective Units of Distress Scale (0–100)[a]	21.1	3.5	13.3	3.9	18.9	6.0	35.6	4.8	45.6	6.8
Women without BPD (n = 10)										
BPD Symptom Scale (0–40)[a,b]	.6	.9	.3	.6	.2	1.1	2.5	1.9	3.2	2.2
Clinician Administered Dissociative States Scale (0–76)[a]	.6	.7	.3	.7	.4	.7	1.1	1.3	1.4	1.5
Fear (analog scale 0–4)[a]	.0	.2	.0	.2	.0	.2	.1	.2	.1	.1
Anxiety (analog scale 0–4)[a]	.4	.3	.1	.2	.1	.3	.6	.3	.9	.4
Subjective Units of Distress Scale (0–100)[a]	12.0	3.3	8.0	3.7	6.5	5.7	19.2	4.5	23.7	6.5

BPD, borderline personality disorder.
[a]Significant main effect for time ($p < .05$).
[b]Significant time-by-diagnosis interaction.

Exposure to scripts of abandonment situations resulted in increased blood flow in right dorsolateral prefrontal cortex (middle and inferior frontal gyrus, areas 10, 46, and 47) in women with BPD (Table 5, Figure 2) but not in women without BPD (Table 3). In the control group, there was a different pattern, with decreased blood flow in left superior frontal gyrus (area 8) as well as right middle and superior frontal gyrus (areas 6, 8, and 10). Direct comparison of activation between women with and without BPD showed that the pattern of activation in bilateral dorsolateral prefrontal cortex was greater in the BPD group (i.e., significant group-by-task interaction; Table 4). We also found increased blood flow in right cuneus (areas 1 and 19) in women with BPD (Table 5, Figure 2), but not in women without BPD (Table 2), with a significant group-by-task interaction for this region (Table 4). The BPD group revealed a region of increased blood flow in right inferior parietal lobe/insula (Table 5, Figure 2).

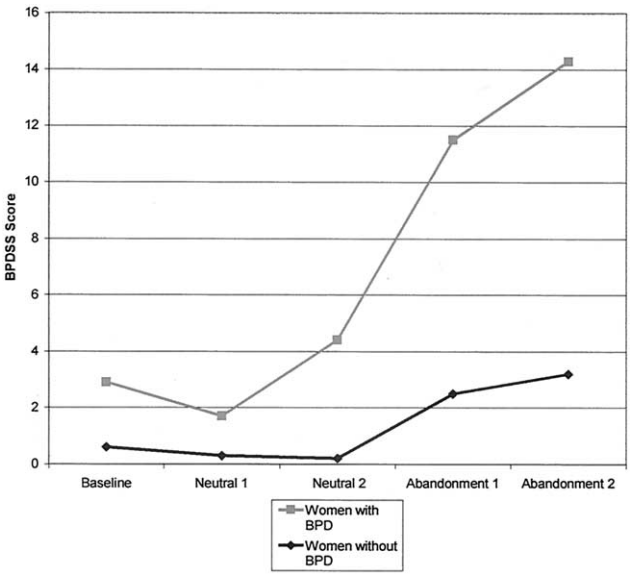

Figure 1. Borderline Personality Disorder Symptom Scale (BPDSS) scores for women with and without borderline personality disorder (BPD) during baseline and during readings of neutral scripts and scripts related to abandonment experience (group-by-time interaction: $F = 3.632$, $df = 4, 68$, $p = .010$)

Exposure to abandonment scripts resulted in decreased blood flow in anterior cingulate bilaterally in women with BPD (areas 24 and 32; Table 5, Figure 3) with greater decreases in this area in BPD compared with control subjects on the right side (i.e., significant group-by-task interaction; Table 4). There was decreased blood flow in several temporal regions in the BPD as well as in the control group (Tables 3 and 5); however, comparison between groups revealed significantly larger decreases in left superior and middle temporal gyrus (areas 21, 22, and 37). We found decreased blood flow in bilateral visual association cortex in women with BPD (Table 5, Figure 3), but not in women without BPD (Table 3). There was a significant group-by-task interaction with greater decreases for left visual association cortex in women with BPD (Table 5). We found significant differences between the groups in the right hippocampus–amygdala region with decreased blood flow in BPD patients (Table 4). There was also decreased blood flow in left fusiform gyrus (areas 36 and 37), motor cortex bilaterally (areas 4 and 6), and right thalamus in the BPD group (Table 5).

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Table 3. Brain Areas of Increased and Decreased Blood Flow during Evoked Abandonment Memories in Women without BPD ($n = 10$)

	Talairach Coordinates			Brodmann's	
z score[a]	x	y	z	Area	Brain Region
Increased Blood Flow					
5.09	54	32	4	45	Right superior frontal gyrus
4.49	62	12	30	44	Right inferior frontal gyrus
2.92	58	18	−14	38	Right superior temporal gyrus
4.01	−24	20	−2	47	Left inferior frontal gyrus
4.00	−26	46	−8	11	Left middle frontal gyrus
3.69	−30	50	−18	11	
3.35	−32	14	24	45	Left inferior frontal gyrus
3.07	−28	8	40		Left medial frontal gyrus
3.01	−24	24	30		
4.12	−54	−8	−22	20	Left inferior temporal gyrus
3.18	−44	6	−20	21	Left middle temporal gyrus
2.67	−58	−12	−38		
3.05	26	−32	14	41	Right inferior parietal lobe
3.03	36	−36	24	40	Right inferior parietal lobe
2.97	22	−22	16	41	
3.92	12	28	32	9	Right anterior cingulate/ medial prefrontal cortex
3.30	12	46	0	32	Right anterior cingulate
2.77	14	48	−20	11	Right orbitofrontal cortex
3.56	−8	−56	48	7	Left precuneus
2.97	−14	−38	32	31	Left posterior cingulate
3.29	12	−100	22		
4.49	46	−80	−42		Cerebellum
3.63	16	−88	−46		
Decreased Blood Flow					
4.29	54	−28	−20	20	Right inferior temporal gyrus
4.15	50	−32	−30	20	
3.20	48	−16	−4	21	Left middle temporal gyrus
3.46	−48	−50	−20	37	Left inferior temporal gyrus
2.99	−30	−32	−24		Cerebellum
3.45	48	−58	10	37	Right middle temporal gyrus
3.28	48	−56	0	37	
2.96	34	12	−38	38	Right superior temporal gyrus
2.85	42	16	−30	38	
3.79	8	−78	6	17	Right lingual gyrus
3.47	12	−42	38	31	Right posterior cingulate
3.46	10	−56	36	7	Right precuneus
3.50	10	16	8		Right caudate
2.96	32	34	−10	11	
2.81	24	22	−4	47	Right inferior frontal gyrus
3.44	26	22	52	6, 8	Right middle/superior frontal gyrus
3.23	2	62	14	10	Right superior frontal gyrus
3.23	−10	38	50	8	Left superior frontal gyrus
2.91	−20	34	50	8	
3.43	−8	−98	−20		Cerebellum
3.39	46	−50	−50		
2.98	38	−46	−48		
2.88	24	−34	−50		
3.30	−42	−70	8	19	Left middle/inferior occipital gyrus
3.22	−8	46	−14	11	Left orbital gyrus
3.05	−6	24	−2	32	Left anterior cingulate
3.10	−54	−32	40	40	Left inferior parietal lobe
2.90	−56	−38	26	40	
2.92	56	−58	40	40	Right inferior parietal lobe
2.78	−40	−38	20	40	Right inferior parietal lobe
2.88	22	−30	−10	35	Right parahippocampal gyrus

BPD, borderline personality disorder.

[a] z Score > 2.58; $p < .005$. Bold numbers indicate primary activation voxels in a cluster; all others indicate other activation within the cluster.

Discussion

Exposure to reminders of abandonment with personalized scripts of abandonment situations resulted in increased activation in the hypothesized area of bilateral dorsolateral prefrontal cortex and decreased activation in the hypothesized areas of left fusiform gyrus, left visual association cortex, and medial prefrontal cortex in women with BPD compared with control subjects. Women with BPD showed alterations in blood flow in other areas that were not hypothesized a priori, including a deactivation in left middle temporal gyrus and an activation in right cuneus. Both groups of women showed deactivation in right precuneus and right caudate, suggesting that this is a generalized neural response to memories of abandonment experiences that is not specific to the pathologic state of BPD.

Our findings of activation in dorsolateral prefrontal cortex are consistent with prior studies using personalized scripts in women with abuse-related PTSD (Bremner et al 1999a; Shin et al 1999). Middle-inferior frontal gyrus has

Table 4. Brain Areas of Greater Increase and Decrease in Blood Flow during Evoked Memories of Abandonment in Women with ($n = 10$) and without ($n = 10$) BPD

	Talairach Coordinates				
z score[a]	x	y	z	Brodmann's Area	Brain Region
Greater Increase in the BPD Group					
3.06	−2	32	56	8	Left superior frontal gyrus
2.86	30	34	−10	11	Right middle frontal gyrus
2.81	24	24	54	6, 8	Right superior frontal gyrus
2.68	44	50	20	9, 10	Right middle frontal gyrus
2.68	46	−60	−2	19, 37	Right inferior temporal gyrus
2.57	16	−40	−10		Cerebellum
2.45	2	−90	36	19	Cuneus
2.40	46	−82	0	19	Right middle occipital gyrus
2.39	12	2	−34	34	
Greater Decrease in the BPD Group					
4.36	46	−78	−46		Cerebellum
2.52	30	−74	−40		
3.39	−52	−34	8	22, 42	Left superior temporal gyrus
3.28	−56	−2	−24	21	Left middle temporal gyrus
2.64	−48	6	−44	21	
3.06	−54	−60	16	37	Left middle temporal gyrus
3.02	−24	42	−10	11	Right medial frontal gyrus
2.54	52	32	4	45	Right inferior frontal gyrus
2.37	4	22	24	24, 32	Right anterior cingulate
2.66	26	−10	−16		Right hippocampus/amygdala
3.26	−46	−68	−12	19	Left visual association cortex
3.15	−50	−78	−20		Cerebellum
2.87	−14	−42	−44		Cerebellum
2.47	−8	−38	−16		Cerebellum
2.34	−2	−80	−34		Cerebellum

BPD, borderline personality disorder.
[a]z Score > 2.33; $p < .01$. Bold numbers indicate primary activation voxels in a cluster; all others indicate other activation within the cluster.

Table 5. Brain Areas of Increased and Decreased Blood Flow during Evoked Abandonment Memories in Women with BPD ($n = 10$)

	Talairach Coordinates				
z score[a]	x	y	z	Brodmann's Area	Brain Region
Increased Blood Flow					
4.39	46	50	16	10, 46	Right middle frontal gyrus
3.36	48	52	2	10	Right inferior frontal gyrus
3.14	56	30	−8	47	Right inferior frontal gyrus
3.12	16	52	4	10	Right medial prefrontal gyrus
3.08	12	48	10	10	
2.37	10	32	14	10, 32	
3.07	6	38	−30	11	Right orbital gyrus
2.99	18	52	−20	11	Right middle frontal gyrus
3.73	6	−94	34	1	Cuneus
3.70	−2	0	−22		Hypothalamus
3.56	20	−30	18		Right inferior parietal lobe
3.29	30	−18	16		Insula
3.25	32	−30	8		
3.47	−16	−2	−48	38	Left Temporal Pole
2.85	−24	24	−32	38	Left superior temporal gyrus
2.63	−30	32	−28	38	
2.36	−38	32	−24	38	
Decreased Blood Flow					
4.57	56	−28	−22	20	Right inferior temporal gyrus
4.27	46	−26	−22	20	
3.55	52	−22	6	42	Right superior temporal gyrus
3.42	−54	10	−8	12, 22	Left superior temporal gyrus
3.15	−56	4	20	4, 6	Left precentral (motor) gyrus
2.84	−54	−4	2	20, 22	Left superior temporal gyrus
3.35	34	12	−34	38	Right superior temporal gyrus
4.36	−42	−52	−10	37	Left fusiform gyrus
3.59	−46	−40	−18	36, 37	
3.38	−24	−32	−40		Cerebellum
4.34	−46	−32	12	42	Left superior temporal gyrus/ visual association cortex
4.34	−52	−40	22	22	
3.43	−52	−58	14	22	
3.86	8	14	8		Right caudate
3.38	6	−14	8		Right thalamus
3.02	32	26	10	24, 32	Right anterior cingulate
2.85	−10	22	−6	32	Left anterior cingulate
3.74	24	−66	30	19	Right visual association cortex
3.69	16	−64	22	31	Precuneus/right superior parietal lobe
3.62	6	−62	6	18	Right lingual gyrus
3.41	−4	−78	−34		Cerebellum
3.05	−20	−70	−40		
3.40	24	−70	−38		Cerebellum
2.91	30	−44	−18		
2.81	42	−48	−50		
3.04	20	8	−16		
3.03	42	−6	48	4	Right precentral gyrus
2.94	40	2	44	6	Right middle frontal gyrus
3.01	−6	44	26	9	Left medial frontal gyrus

BPD, borderline personality disorder.
[a]z Score > 2.58; $p < .005$. Bold numbers indicate primary activation voxels in a cluster; all others indicate other activation within the cluster.

been implicated in encoding and retrieval of verbal memories, with several studies showing a lateralization for encoding on the left and retrieval on the right (Tulving et al 1994). Our findings of greater activation in these prefrontal areas are consistent with the findings of Bremner et al (1999a, 1999b), who also found greater increase in superior and middle frontal gyrus (areas 6 and 9) in PTSD patients. Interestingly, a recent FDG-PET study found activation of right dorsolateral prefrontal cortex in rhesus monkeys after separation from their mothers compared with imaging performed after a period with their mothers (Rilling et al 2001). Thus, the stress of maternal separation seems to activate the same brain region as do memories of childhood abandonment in our patient group.

A number of PET studies have implicated medial prefrontal cortex including anterior cingulate in trauma-related memories (Bremner et al 1999a, 1999b; Liberzon et al 1999; Rauch et al 1996; Shin et al 1997, 1999). Prior studies of healthy subjects also revealed an involvement of this area in stress and emotion (Benkelfat et al 1995; George et al 1995; Lane et al 1997; Reiman et al 1997),

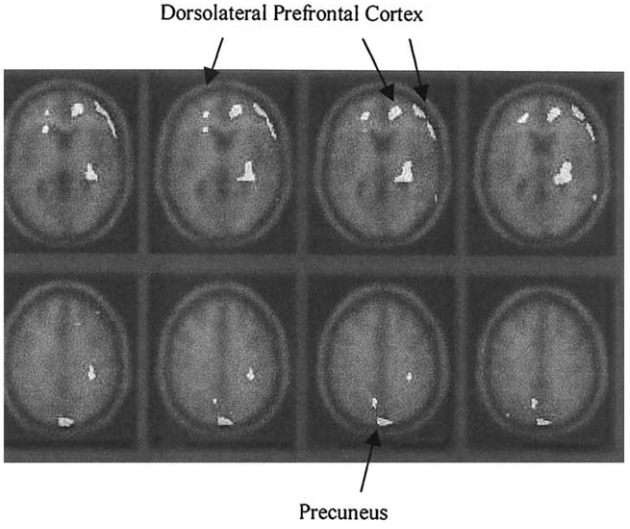

Figure 2. Statistical parametric map overlaid on a magnetic resonance image template, showing areas of significant increase in borderline personality disorder (z score > 2.58, $p < .005$).

and this area has been implicated in the regulation of the peripheral glucocorticoid and sympathetic response to stress (Devinsky et al 1995; Sesack et al 1989; Vogt et al 1992). Medial prefrontal cortex also has inhibitory connections to the amygdala (Devinsky et al 1995; Carmichael and Price 1994, 1995; Sesack et al 1989; Vogt et al 1992) that play a role in extinction of fear responding (Morgan et al 1995). We found greater decrease in blood flow in right anterior cingulate in the BPD group. Dysfunction of medial prefrontal cortex may represent a neural correlate of the generation of pathologic emotion in BPD, including an inability to shut off negative emotions. Two PET studies in healthy adults (Dougherty et al 1999; Kimbrell et al 1999) found increase in blood flow in anterior cingulate during the induction of anger, which is thought to be a key emotion in BPD, and PET studies in BPD (De la Fuente et al 1997; Goyer et al 1994) found decreased function in anterior cingulate. These studies, however, were limited by not using tasks to activate symptoms of BPD. In contrast, our study paradigm may provide information about the specific neural correlates of experiencing of BPD symptoms.

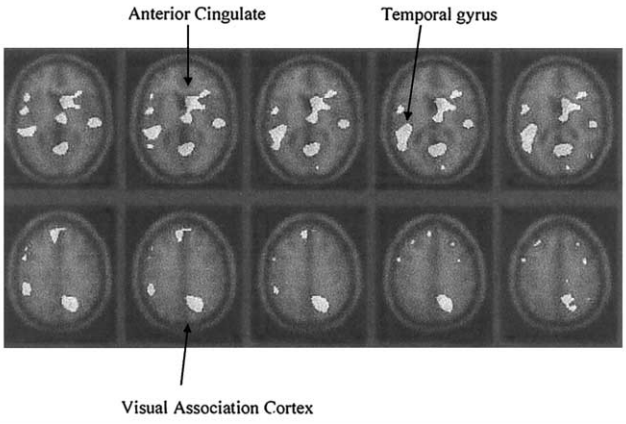

Figure 3. Statistical parametric map overlaid on a magnetic resonance image template, showing areas of significant decrease in borderline personality disorder (z score > 2.58, $p < .005$).

Decreased blood flow was seen in right hippocampus–amygdala region in BPD compared with control women during exposure to scripts of abandonment situations, although not in the BPD group alone. This finding is consistent with our prior study in abuse-related PTSD (Bremner et al 1999a) and unpublished data of patients with abuse-related PTSD during remembrance of emotionally valenced words. Further evidence for impaired function of hippocampus and amygdala in BPD comes from a recent study investigating hippocampal and amygdala volume in patients with BPD (Driessen et al 2000). This investigation found 16% smaller volumes of the hippocampus and 8% smaller volumes of the amygdala compared with healthy control subjects.

We also found decreased blood flow in visual association cortex (area 19) in women with BPD. This finding is consistent with former findings of decreased blood flow in visual association cortex in women with PTSD listening to personalized scripts of childhood sexual abuse (Bremner et al 1999a; Shin et al 1999). There was also deactivation of another brain area involved in complex visual processing, fusiform gyrus, which is specifically involved in memory of faces (George et al 1993). These areas may be involved in visual imagination of abandonment events. It can also be speculated that these areas are involved in visual imagination in trauma-spectrum disorders in general.

There are several possible explanations for activation patterns associated with memories of abandonment in BPD. Our findings may represent neural correlates of memories of abandonment. Also, these findings could be due to an increase in BPD symptomatology while listening to stressful scripts. We cannot exclude the possibility that patients have increased fear, anger, or other emotions associated with memories of abandonment that account for our findings. Differences between BPD patients and control subjects in stressful memories in general and differences in their ability to memorize fearful events could also contribute to these findings.

There is a large overlap between PTSD and BPD regarding etiology as well as clinical presentation of these disorders. Prevalence of childhood physical and sexual abuse ranges from 29–71% (Zanarini 1997), and about 50% of patients with BPD fulfill the diagnostic criteria for PTSD (McGlashan et al 2000). Clinically, the frequent

stress-related symptoms in patients with BPD, such as anxiety and dissociative phenomena, also underline the overlap between BPD and other trauma spectrum disorders such as PTSD. Future studies should include a PTSD comparison group to test for differences between these two trauma-related disorders.

Several limitations have to be considered in interpreting our results. First, this was a pilot study investigating abandonment memories in women with BPD and was limited in sample size. Second, nearly all BPD subjects were taking psychotropic medication during the investigation. In our experience, it is nearly impossible to recruit BPD patients without psychotropic medication. Antidepressants and neuroleptics influence brain metabolism and reactivity to stressful reminders; however, it seems to be unlikely that the medication could lead to specific increases and decreases as seen in our study. Rather, it would lead to a more generalized effect. Third, we did not match the two groups for the presence of Axis I disorders. There was a higher rate of comorbid psychiatric disorders in patients with BPD. Comorbid depressive disorder and PTSD may have an influence on our findings; however, exclusion of comorbid PTSD would lead to a sample not representative for BPD with its high rate of traumatic experience. The sample size of our study was not large enough to perform an analysis of subgroups (e.g., with and without PTSD). Future studies are needed with a larger sample size and a comparison between subgroups of BPD patients. Also, future studies should investigate memories of abandonment in a healthy control group. A further limitation of our study was the fact that we compared personalized abandonment scripts with standardized, nonpersonalized neutral scripts. We chose standardized neutral scripts because it appeared difficult to find emotionally neutral personalized situations in patients with BPD. The ability to visualize the content of the scripts was not controlled for in our study. Thus, individual differences in visualization may have influenced our results. Also, differences in attention were not controlled for in our study. Because we did not correct our results for multiple comparisons, there exists the possibility that some of the regions found to be significant may be due to false positive findings. Finally, a fixed-effects analysis was employed in this analysis, which will limit the ability to generalize from the study population.

This is the first neuroimaging study of stressful reminders in borderline personality disorder and the first investigating neural correlates of abandonment. Prefrontal and limbic areas, which play a major role in other psychiatric conditions such as PTSD, seem to be involved in emotional stress in patients with BPD. The findings raise the question of whether there is a common neural circuitry in trauma-related psychiatric disorders. The question arises of why stress results in different phenotypic expressions of these disorders if the circuitry is similar.

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