A Positron Emission Tomography Study of Memories of Childhood Abuse in Borderline Personality Disorder

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Background: *Borderline personality disorder (BPD) is a common psychiatric disorder, which is linked to early stressors in many cases; however, the impact of traumatic events in the etiology of BPD is still unclear. This pilot study was conducted to measure the neural correlates of recall of traumatic memories in women with and without BPD.*

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

Results: *Memories of trauma were associated with increases in blood flow in right dorsolateral prefrontal cortex (Brodmann's area [BA] 44 and 45) and with decreased blood flow in left dorsolateral prefrontal cortex (BA 44 and 45) in women without BPD. There was also increased blood flow in right anterior cingulate (BA 24) and left orbitofrontal cortex (BA 11) in women without BPD. Women with BPD failed to activate anterior cingulate gyrus and orbitofrontal cortex. Also, no blood flow changes were seen in dorsolateral prefrontal gyrus in women with BPD.*

Conclusions: *Dysfunction of dorsolateral and medial prefrontal cortex, including anterior cingulate, seems to be correlated with the recall of traumatic memories in women with BPD. These brain areas might mediate trauma-related symptoms, such as dissociation or affective instability, in patients with BPD.*

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

Borderline personality disorder (BPD) is a highly prevalent condition that affects 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. One of the most important psychosocial factors involved in the development of BPD is childhood sexual and/or physical abuse (Zanarini 1997). In five controlled studies of BPD (Herman et al 1989; Links et al 1988; Ogata et al 1990; Westen et al 1990; Zanarini et al 1989) prevalence of childhood physical abuse ranges between 29% and 71%. Sexual abuse in childhood was experienced by 52% (Westen et al 1990) to 71% (Ogata et al 1990) of BPD patients—significantly more than by control subjects. Given these numbers and the frequent trauma-related symptoms in borderline patients, such as dissociative phenomena, BPD has been suggested to be part of a spectrum of trauma-associated disorders (Bremner 2002).

Recently, neurobiological studies have begun searching for common or overlapping features between different trauma-spectrum disorders. Volumetric studies have found evidence for a reduction in hippocampus and amygdala volume in patients with BPD and early abuse (Driessen et al 2000; Tebartz van Elst et al 2003) that parallel findings of reduced volumes of these regions in patients with posttraumatic stress disorder (PTSD). We also found a 21.9% smaller mean amygdala volume and a 13.1% smaller hippocampal volume in patients with BPD and early trauma compared with control subjects (Schmahl et al 2003b). These studies suggest that BPD with early abuse, similar to PTSD with early abuse, is associated with smaller hippocampal volume. Studies to date suggest that abuse without any psychiatric disorder is not associated with hippocampal volume reduction (Gurvits et al 1996; Bremner et al, unpublished data), whereas abuse with a variety of psychiatric disorders, including PTSD (Bremner et al 1997; Stein et al 1997), depression (Vythilingam et al 2002), and BPD are associated with volume reduction.

Neuroimaging studies in PTSD after childhood abuse have demonstrated abnormalities in prefrontal brain areas. Shin et al (1999) found greater increases in orbitofrontal cortex and greater decreases in anterior prefrontal cortex in patients with PTSD as compared with control subjects. A positron emission tomography (PET) study of abuse-related memories in women with a history of childhood sexual abuse revealed greater increases in blood flow in the dorsolateral prefrontal cortex (Brodmann's areas [BA] 6 and 9), posterior cingulate (BA 31), and motor cortex, as well as a failure of activation in anterior cingulate (BA 32) in women with PTSD compared with women without PTSD (Bremner et al 1999a). Using the method of script-driven symptom provocation in conjunction with functional magnetic resonance imaging, Lanius et al (2001, 2003) found decreased function in medial prefrontal cortex, anterior cingulate, and thalamus in patients with PTSD.

Functional neuroimaging studies of BPD patients have been limited, and findings have not been consistent. De la Fuente et al (1997), using [18 F]fluorodeoxyglucose (FDG)-PET, found decreased metabolism in premotor and prefrontal areas and in anterior cingulate cortex in BPD patients as compared with control subjects. In contrast, Juengling et al (2003) found increased baseline metabolism in anterior cingulate and dorsolateral prefrontal cortex in BPD patients also measured with FDG-PET. We measured brain blood flow in response to scripts describing situations of abandonment in women with and without BPD (Schmahl et al 2003a). Memories of abandonment were associated with greater increases in blood flow in bilateral

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

	SCID Current Diagnoses	SCID Lifetime Diagnoses[a]	Psychotropic Medication
Control Subjects			
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 Patients			
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, cocain abuse	Bupropion, divalproex sodium
6	MDD, body dismorphic disorder, bulimia nervosa	MDD, body dismorphic disorder, bulimia nervosa, alcohol dependence	None
7	None	Bipolar I disorder, alcohol abuse, polysubstance dependence	Gabapentine, olarizapine
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

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

dorsolateral prefrontal cortex (middle frontal gyrus, BA 9 and 10) and right cuneus (BA 19) in women with BPD than in women without BPD. Abandonment memories were associated with greater decreases in right anterior cingulate (BA 24 and 32) in women with BPD than in women without BPD. A larger decrease in blood flow in women with BPD was also seen in left temporal cortex and left visual association cortex.

Because we were interested in the impact of trauma and trauma-related memories in borderline personality disorder, the present study was conducted with PET in the examination of neural correlates of trauma memories in patients with BPD. On the basis of the findings described above for abuse-related PTSD, we hypothesized that exposure to traumatic scripts would result in a failure of activation in anterior cingulate and in alterations in blood flow 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 and the Human Studies Subcommittee of the U.S. Department of Veterans Affairs (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. The same subjects participated in our PET study of neural correlates of abandonment; data from that study have been previously reported (Schmahl et al 2003a).

All subjects were recruited through newspaper and flyer advertisements. 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 with 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, 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; eight of the 10 BPD subjects were taking antidepressant or neuroleptic medication, and two were medication free; no subject was taking benzodiazepine medication. Table 1 lists psychotropic medica-

tion and 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, or a history of head trauma, loss of consciousness, cerebral infectious disease, or dyslexia were excluded. There were no significant differences in age between the BPD (mean = 30 years) and control subjects (mean = 33 years). All BPD participants and 9 out of 10 control participants were right-handed.

History of childhood abuse was assessed with the Early Trauma Inventory, self-report version (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; however, retrospective self-reports of abuse have to be judged with the usual caveats. Mean ETI score in the BPD group was 73.8; mean ETI score in the control group was 61.3 (ns).

Procedure

The procedure has been described in detail elsewhere (Schmahl et al 2003a). In brief, two personalized scripts of situations of childhood sexual or physical abuse were prepared, each 1 min in length, which were later read aloud to the subject during the scanning session by a research assistant who was blind to the diagnostic status of the subject. Each subject underwent four scans on a single day during readings of neutral and trauma scripts. First, subjects underwent two scans while listening to two different nonpersonalized neutral narratives, which were identical for all participants, preceded by instructions to listen carefully and form an image in their mind. Then subjects underwent two scans, during which they listened to two personalized scripts of their own traumatic event. Between these two types of scripts, two scripts of situations of abandonment were read to the subjects (data reported elsewhere [Schmahl et al 2003a]). At the same time as the beginning of the script reading, 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.

Image Analysis

Images were reconstructed and analyzed on a Sun Sparc workstation (Sun Microsystems, Santa Clara, California) 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 trauma and neutral script conditions for the women with and without BPD. The interaction between group (BPD vs. non-BPD) and condition (trauma 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). 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, we performed analyses of activation patterns on a whole-brain basis for exploratory purposes to generate hypotheses for future studies in BPD. Location of areas of activation was identified as the distance from the anterior commissure in millimeters, with x, y, and z coordinates; a standard stereotaxic atlas was used to identify regions of activation (Talairach and Tournoux 1988).

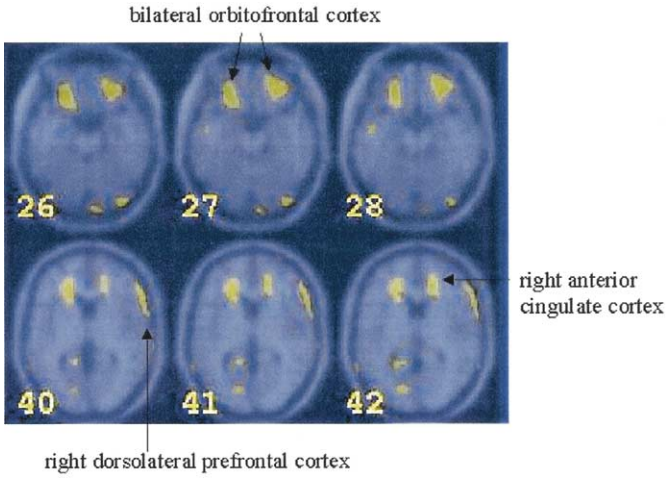

Figure 1. Statistical parametric map overlaid on a magnetic resonance image template, showing areas of significant increase in women without borderline personality disorder (*Z* score > 2.58, $p < .005$).

Results

Deactivation in right precuneus (BA 7) and right caudate with recall of traumatic memories was nonspecifically seen both in women with and in women without BPD. In the control group and in the BPD group we found several regions of activation and deactivation in the cerebellum (Tables 2 and 3).

Exposure to scripts of trauma situations resulted in increased blood flow in right anterior cingulate (BA 24), right dorsolateral

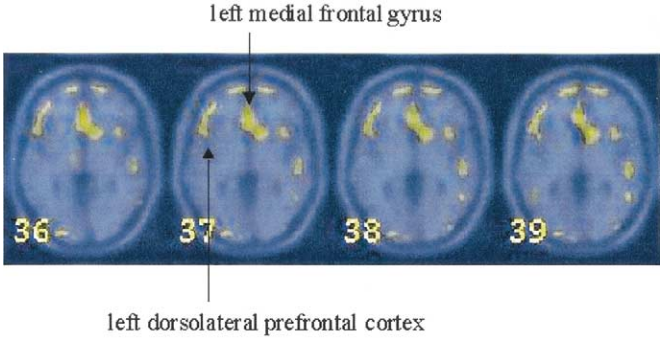

Figure 2. Statistical parametric map overlaid on a magnetic resonance image template, showing areas of significant decrease in women without borderline personality disorder (*Z* score > 2.58, $p < .005$).

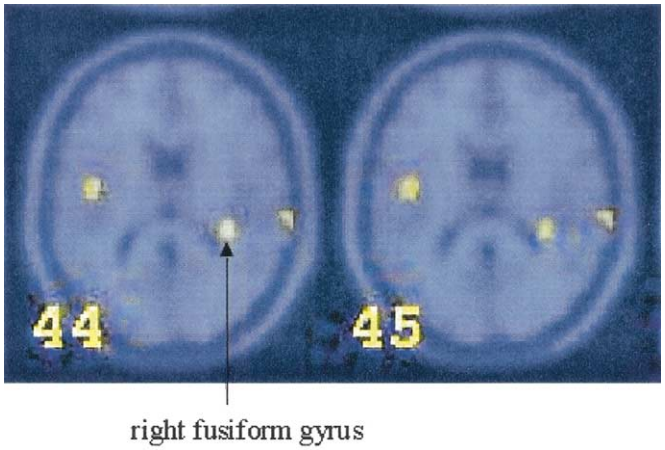

Figure 3. Statistical parametric map overlaid on a magnetic resonance image template, showing areas of significant increase in women with borderline personality disorder (Z score > 2.58, $p < .005$).

prefrontal cortex (inferior frontal gyrus, BA 44 and 45), and bilateral orbitofrontal cortex (BA 11) in women without BPD (Table 2; Figure 1) but not in women with BPD (Table 3). Deactivation was seen in right fusiform gyrus (BA 36 and 37), left medial frontal gyrus (BA 9), right posterior cingulate (BA 31), and left dorsolateral prefrontal cortex (inferior frontal gyrus, BA 44 and 45) in the control group (Table 2; Figure 2). Again, these regions could not be shown to be deactivated in the BPD group (Table 3).

Patients with BPD had increased blood flow in left medial prefrontal gyrus (BA 6) and right fusiform gyrus (BA 19; Figure 3). Decreased blood flow was found in left orbitofrontal cortex (medial frontal gyrus, BA 10; superior frontal gyrus, BA 11) and in the right hippocampal region (BA 24) in BPD patients (Table 3; Figure 4).

Direct comparison of activation between women with and without BPD (Table 4) showed that the pattern of deactivation in right anterior cingulate was greater in the BPD group, which is owing to the failure of activation in this region in the BPD patients as compared with control subjects. Also, greater decreases in blood flow were found in orbitofrontal cortex bilaterally. Again, this is owing to a failure of activation in right orbitofrontal cortex and to decreased blood flow in left orbitofrontal cortex in patients with BPD.

Discussion

Recall of traumatic memories was associated with increases in blood flow in right dorsolateral prefrontal cortex and decreased blood flow in left dorsolateral prefrontal gyrus in women without BPD. There was also increased blood flow in right anterior cingulate and orbitofrontal cortex bilaterally in women without BPD. Women with BPD failed to activate anterior cingulate gyrus and orbitofrontal cortex. This failure of activation resulted in a relative decrease in the BPD group as compared with control subjects (Table 4). Also, no blood flow changes were seen in dorsolateral prefrontal gyrus in women with BPD.

A number of PET studies have implicated medial prefrontal

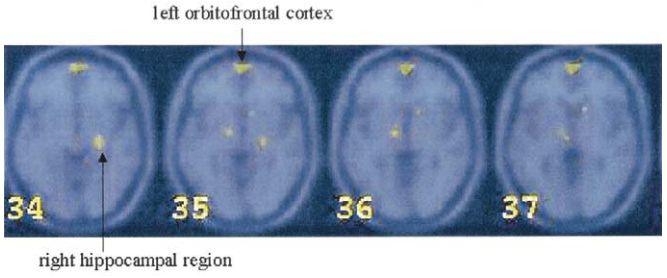

Figure 4. Statistical parametric map overlaid on a magnetic resonance image template, showing areas of significant decrease in women with borderline personality disorder (Z score > 2.58, $p < .005$).

Table 2. Brain Areas of Increased and Decreased Blood Flow during Evoked Traumatic Memories in 10 Women Without Borderline Personality Disorder

	Talairach Coordinates			Brodmann's	
Z Score[a]	x	y	z	Area	Brain Region
Increased Blood flow					
5.03[b]	14	30	20	24	Right anterior cingulate
4.58[b]	−38	−84	24	19	Left occipital lobe
3.91	−16	−50	44	7	Left precuneus
3.90	−22	−50	22		
4.57[b]	60	32	6	45	Right inferior frontal gyrus
4.24	60	18	−4		
3.64	62	20	26	44, 45	Right inferior frontal gyrus
4.56[b]	−22	30	12		Left frontal lobe
3.85	−24	30	−16	11	Left orbitofrontal
3.75	−16	18	−28	11	Left orbitofrontal
4.34[b]	28	40	−20	11	Right orbitofrontal
4.11[b]	18	−92	−36		Cerebellum
3.86	40	−90	−24		Cerebellum
3.31	50	−78	−34		Cerebellum
3.85[b]	34	−50	28		Right parietal lobe
3.60	32	−36	30		Right parietal lobe
3.23	42	−28	28		Right parietal lobe
3.55[b]	−52	−20	−8	21	Left middle temporal gyrus
3.51[b]	−68	−22	28	2	Left postcentral gyrus
3.13	−70	−28	22	40	Left inferior parietal lobe
2.94	−68	−12	18	2, 43	Left postcentral gyrus
Decreased Blood Flow					
4.63[b]	34	−34	−16	36, 37	Right fusiform gyrus
4.48	50	−44	−22	37	Right fusiform gyrus
4.46	34	−48	−38		Cerebellum
4.53[b]	−2	48	38	9	Left medial frontal gyrus
4.36	12	14	4		Right caudate
4.13	−4	32	54	8	Left superior frontal gyrus
4.16[b]	10	−54	30	31	Right posterior cingulate
3.34	6	−42	44	31	Right posterior cingulate
2.91	12	−70	42	7	Right precuneus
4.15[b]	40	−86	20	19	Right occipital lobe
3.66	40	−88	8	18	Right occipital lobe
4.15[b]	56	−62	44	40	Right inferior parietal lobe
3.97[b]	−6	−28	−50		
3.94[b]	−54	24	10	45	Left inferior frontal gyrus
3.72	−44	40	0	44	Left inferior frontal gyrus
2.87	−42	10	4		Left insula
3.93[b]	−50	−60	14	37, 39	Left middle temporal gyrus
3.60	−48	−34	26	40	Left inferior parietal lobe
3.55[b]	42	−4	26		Right frontal lobe

[a] Z score > 2.58, $p < .005$.
[b] Primary activation voxels in a cluster. Voxels below indicate other activation within the cluster.

Table 3. Brain Areas of Increased and Decreased Blood Flow during Evoked Trauma Memories in 10 Women with Borderline Personality Disorder

	Talairach Coordinates			Brodmann's	
Z Score[a]	x	y	z	Area	Brain Region
Increased Blood Flow					
3.36[b]	−58	−30	54	40	Left Inferior parietal lobe
3.31[b]	−44	−8	18	43	
2.71	−56	−20	24	2	Left gyrus postcentralis
3.30[b]	−54	−58	44	40	Left Inferior parietal lobe
3.18[b]	34	−34	12	41	Right temporal lobe
3.06[b]	−14	−18	48	6	Left medial frontal gyrus
3.00[b]	70	−28	14	22	Right superior temporal gyrus
2.96	64	−24	20	40	Right gyrus postcentralis
2.85[b]	46	−62	−10	19	Right fusiform gyrus
2.84[b]	60	12	30	9	Right inferior frontal gyrus
2.75[b]	58	−6	52	6	
2.72[b]	14	−22	22		
2.54[b]	16	12	44	6	Right superior frontal gyrus
2.53[b]	50	46	16		Right inferior frontal gyrus
Decreased Blood Flow					
4.09[b]	−20	−68	−48		Cerebellum
3.66	−2	−76	−44		Cerebellum
3.92[b]	28	10	−42	38	Right middle temporal gyrus
2.54	46	18	−34	38	Right superior temporal gyrus
3.62[b]	20	−54	34	7	Right precuneus
3.41	24	−74	36	7, 19	
3.10	26	−86	34	19	Right superior occipital gyrus
3.55[b]	0	64	−2	10	Medial frontal gyrus
3.38	−10	60	−18	11	Left superior frontal gyrus/ orbitofrontal
3.48[b]	52	−72	20	39	Right middle temporal gyrus
3.35[b]	−40	−46	−50		Cerebellum
3.34[b]	24	−18	−10		Right hippocampal region
3.14	44	−26	−28	20	Right frontal gyrus
2.97	60	−22	−32	20	Right frontal gyrus
3.03[b]	18	−14	−38		
3.02[b]	−14	−32	−20		Cerebellum
3.02[b]	−34	−74	30	19	
2.98[b]	18	−38	−50		Cerebellum
2.56	0	−36	−50		Cerebellum

[a] *Z* score > 2.58, $p < .05$.
[b] Primary activation voxels in a cluster. Voxels below indicate other activation within the cluster.

Table 4. Brain Areas of Greater Increase and Decrease in Blood Flow during Evoked Trauma Memories in 10 Women with than in 10 without Borderline Personality Disorder (BPD)

	Talairach Coordinate			Brodmann's	
Z Score[a]	x	y	z	Area	Brain Region
Greater Increase in the BPD Group					
4.10[b]	50	−44	−20	20, 37	Right inferior temporal gyrus
3.28	48	−58	−40		
3.14	38	−66	−50		Cerebellum
3.91[b]	−44	−10	20	43	Left parietal lobe
3.18	−48	−34	28	40	Left inferior parietal lobe
2.90	−42	6	6		Left insula?
3.90[b]	24	28	52	8	Right superior frontal gyrus
3.74	−4	32	54	8	Left superior frontal gyrus/ orbitofrontal
3.73	−2	48	38	8	Left medial frontal gyrus
3.61[b]	56	−62	44	40	Right inferior parietal lobe
3.44[b]	42	−84	22	19	Right medial temoral gyrus
2.68	40	−88	8	19	Right medial occipital gyrus
3.34[b]	−48	30	18	45, 46	Left middle frontal gyrus
3.27[b]	42	−4	22	4	Right frontal lobe
3.19[b]	38	12	2		Right insula
3.01[b]	10	0	14		Right caudate
2.87[b]	−22	44	32	9	Left superior frontal gyrus
2.83[b]	20	−70	−34		Cerebellum
2.77[b]	−52	−4	42	6	
Greater Decrease in the BPD Group					
4.61[b]	−34	−76	26	19	Left middle occipital gyrus
3.61	−24	−58	46	7	Left parietal lobe
3.59	−12	−78	14	17, 18	Left cuneus
4.10[b]	−52	−22	−8	21	Left middle temporal gyrus
3.84[b]	−26	28	−30		
3.65	−20	30	10		Fasciculus occipito-frontalis
2.86	−20	48	−18	11	Left orbitofrontal
3.80[b]	14	30	22	24	Right anterior cingulate
3.73[b]	30	−54	30		Right parietal lobe
2.92	44	−28	28		Right parietal lobe
2.44	34	−24	32		Right parietal lobe
3.61[b]	56	−72	20	39	Right middle temporal gyrus
3.60[b]	16	−92	−36		Cerebellum
3.42[b]	−18	−48	−50		Cerebellum
3.34[b]	−48	−42	−50		Cerebellum
3.34[b]	32	38	−20	11	Right orbitofrontal
3.29[b]	−16	54	−20	11	Left orbitofrontal
3.29[b]	60	16	−2		
3.26	60	32	6	45	Right inferior frontal gyrus
2.66	58	28	26	46	Right middle frontal gyrus

[a] *Z* score > 2.33, $p < .01$.
[b] Primary activation voxels in a cluster. Voxels below indicate other activation within the cluster.

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 in 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), 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 (Carmichael and Price 1994, 1995; Devinsky et al 1995; Sesack et al 1989; Vogt et al 1992) that play a role in extinction of fear responding (Morgan et al 1995). Moreover, medial prefrontal cortex neurons could also be shown to store long-term extinction memory (Milad and Quirk 2002). Failure of activation in anterior cingulate, as found in the present study, is in good agreement with studies in patients with PTSD challenged by traumatic scripts (Bremner et al 1999a; Lanius et al 2001, 2003) and our own study in patients with BPD, which revealed greater decrease in blood flow in right anterior cingulate in response to abandonment scripts. Dysfunction of medial prefrontal cortex might represent a neural correlate of the generation of pathologic emotion in BPD, including an inability to shut off negative emotions. In an FDG-PET study, we found elevated baseline metabolism in patients with BPD as compared with control subjects (Juengling et al 2003). It might be speculated that BPD patients have elevated resting function in the anterior cingulate, with a failure in the normal cingulate response to emotional stimuli.

In contrast to our previous findings of activation in dorsolateral

prefrontal cortex in response to abandonment scripts, in the present study BPD patients did not reveal increased or decreased blood flow in dorsolateral prefrontal areas. Middle/inferior frontal gyrus has 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 right inferior frontal gyrus in the control group might be related to an effort to retrieve traumatic memories. It might be speculated that women with BPD do not actively retrieve traumatic memories or even suppress them.

Decreased blood flow was seen in the right hippocampal region in women with BPD during exposure to traumatic memories; such a decrease was not found in the control group. This finding is consistent with our prior studies in abuse-related PTSD (Bremner et al 1999a, 2003) and our prior study with memories of abandonment in BPD patients (Schmahl et al 2003a). Further evidence for impaired function of the hippocampus in BPD comes from recent findings of reduced hippocampal volume in patients with BPD (Driessen et al 2000; Schmahl et al 2003b; Tebartz van Elst et al 2003). Given the known role of the hippocampus in mediating emotional processing of complex visual stimuli (Kim and Fanselow 1992; Phillips and LeDoux 1992) it is not surprising that this region is involved in processing traumatic memories in PTSD and BPD.

In a similar fashion as in right anterior cingulate, activation in left orbitofrontal cortex was seen in traumatized women without BPD but not in the BPD group (Tables 2, 3, and 4). Orbitofrontal cortex and a cortical–subcortical circuit involving orbitofrontal regions seem to play a significant role in social cognition (Baron-Cohen 1995; Baron-Cohen et al 1994). Patients with orbitofrontal lesions exhibit behavioral disinhibition, affective dysregulation, and social cognition deficits (Blair and Cipolotti 2000; Damasio 1994; Stone et al 1998), all of which are also typical features of BPD. Failure of activation in this area might represent an inability to recognize or to correctly interpret social cues.

There are several possible explanations for activation patterns associated with traumatic memories in BPD. Our findings may represent neural correlates of recalling traumatic memories. Also, these findings could be due to an increase in BPD symptomatology while listening to stressful scripts. We cannot exclude the fact that patients have increased fear, anger, or other emotions that account for the findings of the current study. 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.

Several limitations have to be considered in interpreting our results. First, this was a pilot study investigating traumatic 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 who are not taking 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 the specific increases and decreases 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 might 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 big 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. A further limitation of our study was that we compared personalized trauma scripts with standardized, nonpersonalized neutral scripts. We chose standardized neutral scripts because it seemed difficult to find emotionally neutral personalized situations in patients with BPD. Also, we cannot rule out the possibility of an order effect. The ability to visualize the content of the scripts was not controlled for in our study. Thus, individual differences in visualization might 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 might be due to false-positive 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 between 29% and 71% (Zanarini 1997), and approximately 50% of patients with BPD fulfill the diagnostic criteria for PTSD (McGlashan et al 2000). There is an ongoing discussion as to whether BPD represents a form of complex or chronic PTSD (Bremner 2002) or belongs to a spectrum of "disorders of extreme stress not otherwise specified" (Herman 1993). Clinically the frequent stress-related symptoms in borderline patients, such as anxiety and dissociative phenomena, also underline the overlap between BPD and other trauma-spectrum disorders like PTSD. As outlined in the introduction, several findings point at common or overlapping neurobiological correlates of these two disorders. Because the activation pattern found in the present study seems to be similar to activation patterns found in PTSD patients listening to traumatic scripts, it can be concluded that traumatic memories involve similar circuits in both disorders. When these findings are taken together, the conceptualization of a spectrum of trauma-related disorders, as proposed by Bremner (2002), seems to be justified. On the other hand, compared with the activation pattern found during abandonment memories in patients with BPD (Schmahl et al 2003a), memories of traumatic episodes elicited a somewhat different pattern of activation, with less activation in prefrontal areas. Thus, it can be concluded that traumatic stress is an important factor in the development of BPD but that other types of interpersonal stress (e.g., situations of abandonment), might be of similar importance for the development of BPD. To test this hypothesis directly, a comparison study of the two diagnostic groups with the use of different types of stress-related scripts would be necessary.

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Baron-Cohen S (1995): *Mindblindness: An Essay on Autism and Theory of Mind*. Cambridge, Massachusetts: MIT Press.

Baron-Cohen S, Ring H, Moriarty J, Schmitz B, Costa D, Ell P (1994): Recognition of mental state terms: Clinical findings in children with autism and a functional neuroimaging study of normal adults. *Br J Psychiatry* 165:640–649.

Benkelfat C, Bradwejn J, Meyer E, Ellenbogen M, Milot S, Gjedde A, Evans A (1995): Functional neuroanatomy of CCK sub 4-induced anxiety in normal healthy volunteers. *Am J Psychiatry* 152:1180–1184.

Blair RJR, Cipolotti L (2000): Impaired social response reversal. A case of "acquired sociopathy." *Brain* 123:1122–1141.

Bremner JD (2002): *Does Stress Damage the Brain? Understanding Trauma-Related Disorders from a Mind-Body Perspective*. New York: WW Norton.

Bremner JD, Narayan M, Staib LH, Southwick SM, McGlashan T, Charney DS (1999a): Neural correlates of childhood sexual abuse in women with

and without posttraumatic stress disorder. *Am J Psychiatry* 156:1787–1795.

Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, et al (1997): Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. *Biol Psychiatry* 41:23–32.

Bremner JD, Staib LH, Kaloupek D, Southwick SM, Soufer R, Charney DS (1999b): Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: A positron emission tomography study. *Biol Psychiatry* 45:806–816.

Bremner JD, Vermetten E, Mazure CM (2000): Development and preliminary psychometric properties of an instrument for the measurement of childhood trauma: The early trauma inventory. *Depress Anxiety* 12:1–12.

Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, et al (2003): MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *Am J Psychiatry* 160:924–932.

Carmichael ST, Price JL (1994): Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. *J Comp Neurol* 346:366–402.

Carmichael ST, Price JL (1995): Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *J Comp Neurol* 363:615–641.

Damasio AR (1994): *Descartes' Error: Emotion, Reason and the Human Brain*. New York: Putnam.

De la Fuente JM, Goldman S, Stanus E, Vizuette C, Morlán I, Bobes J, Mendlewicz J (1997): Brain glucose metabolism in borderline personality disorder. *J Psychiatr Res* 31:531–541.

Devinsky O, Morrell MJ, Vogt BA (1995): Contributions of anterior cingulate to behavior. *Brain* 118:279–306.

Driessen M, Herrmann J, Stahl K, Zwaan M, Meier S, Hill A, et al (2000): Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Arch Gen Psychiatry* 57:1115–1122.

Friston K, Frith C, Liddle P, Frackowiak R (1991): Comparing functional (PET) images: The assessment of significant change. *J Cereb Blood Flow Metab* 11:690–699.

George MS, Ketter TA, Parekh PI, Horwitz B, Herscovitch P, Post RM (1995): Brain activity during transient sadness and happiness in healthy women. *Am J Psychiatry* 152:341–351.

Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, et al (1996): Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biol Psychiatry* 40:1091–1099.

Herman JL (1993): Posttraumatic stress disorder: DSM IV and beyond. In: Davidson JRT, Foa EB, editors. *Posttraumatic Stress Disorder: DSM IV and Beyond.* Washington, DC: American Psychiatric Press, 213–288.

Herman JL, Perry JC, van der Kolk BA (1989): Childhood trauma in borderline personality disorder. *Am J Psychiatry* 146:490–495.

Juengling FD, Schmahl CG, Heβlinger B, Ebert D, Bremner JD, Gostomzyk J, et al (2003): Positron emission tomography in female patients with Borderline Personality Disorder. *J Psychiatr Res* 37:109–115.

Kim JJ, Fanselow MS (1992): Modality-specific retrograde amnesia of fear. *Science* 256:675–677.

Lane RD, Reiman EM, Ahern GL, Schwartz GE, Davidson RJ (1997): Neuroanatomical correlates of happiness, sadness, and disgust. *Am J Psychiatry* 154:926–933.

Lanius RA, Williamson PC, Densmore M, Boksman K, Gupta MA, Neufeld RW, et al (2001): Neural correlates of traumatic memories in posttraumatic stress disorder: A functional MRI investigation. *Am J Psychiatry* 158:1920–1922.

Lanius RA, Williamson PC, Hopper J, Densmore M, Boksman K, Gupta MA, et al (2003): Recall of emotional states in posttraumatic stress disorder: An fMRI investigation. *Biol Psychiatry* 53:204–210.

Liberzon I, Taylor SF, Amdur R, Jung TD, Chamberlain KR, Minoshima S, et al (1999): Brain activation in PTSD in response to trauma-related stimuli. *Biol Psychiatry* 45:817–826.

Links PS, Steiner M, Offord DR, Eppel A (1988): Characteristics of borderline personality disorder: A Canadian study. *Can J Psychiatry* 33:336–340.

McGlashan TH, Grilo CM, Skodol AE, Gunderson JG, Shea MT, Morey LC, et al (2000): The Collaborative Longitudinal Personality Disorders Study: Baseline axis I/II and II/II diagnostic co-occurence. *Acta Psychiatr Scand* 102:256–264.

Milad MR, Quirk GJ (2002): Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature* 420:70–74.

Morgan MA, LeDoux JE (1995): Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Behav Neurosci* 109:681–688.

Ogata SN, Silk KR, Goodrich S, Lohr NE, Westen D, Hill EM (1990): Childhood sexual and physical abuse in adult patients with borderline personality disorder. *Am J Psychiatry* 147:1008–1013.

Phillips RG, LeDoux JE (1992): Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behav Neurosci* 106:274–285.

Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, et al (1996): A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch Gen Psychiatry* 53:380–387.

Reiman EM, Lane RD, Ahern GL, Schwartz GE, Davidson RJ, Friston KJ, et al (1997): Neuroanatomical correlates of externally and internally generated human emotion. *Am J Psychiatry* 154:918–925.

Schmahl CG, Elzinga BM, Vermetten E, Sanislow C, McGlashan TH, Bremner JD (2003a): Neural correlates of memories of abandonment in women with and without borderline personality disorder. *Biol Psychiatry* 54:142–151.

Schmahl CG, Vermetten E, Elzinga BM, Bremner JD (2003b): Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. *Psychiatry Res: Neuroimaging* 122:109–115.

Sesack SR, Deutch AY, Roth RH, Bunney BS (1989): Topographic organization of the efferent projections of the medial prefrontal cortex in the rat: An anterograde tract-tracing study using phaseolus vulgaris leucoagglutinin. *J Comp Neurol* 290:213–242.

Shin LM, Kosslyn SM, McNally RJ, Alpert NM, Orr SP, Savage CR, et al (1997): Visual imagery and perception in posttraumatic stress disorder: A positron emission tomographic investigation. *Arch Gen Psychiatry* 54:233–241.

Shin LM, McNally RJ, Kosslyn SM, Thompson WL, Rauch SL, Alpert NM, et al (1999): Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: A PET investigation. *Am J Psychiatry* 156:575–584.

Spitzer RL, Williams JBW, Gibbon M (1995): *Structured Clinical Interview for DSM-IV (SCID)*. New York: New York State Psychiatric Institute, Biometrics Research.

Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B (1997): Hippocampal volume in women victimized by childhood sexual abuse. *Psychol Med* 27:951–959.

Stone VE, Baron-Cohen S, Knight RT (1998): Frontal lobe contributions to theory of mind. *J Cogn Neurosci* 10:640–656.

Talairach J, Tournoux P (1988): *Co-Planar Sterotaxic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Cerebral Imaging*. New York: Thieme.

Tebartz van Elst L, Hesslinger B, Thiel T, Geiger E, Haegele K, Lemieux L, et al (2003): Frontolimbic brain abnormalities in patients with borderline personality disorder. A volumetric MRI study. *Biol Psychiatry* 54:163–171.

Torgersen S, Kringlen E, Cramer V (2001): The prevalence of personality disorders in a community sample. *Arch Gen Psychiatry* 58:590–596.

Tulving E, Kapur S, Craik FIM, Moscovitch M, Houle S (1994): Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings. *Proc Natl Acad Sci U S A* 91:2016–2020.

Vythilingam M, Heim C, Newport CD, Miller AH, Vermetten E, Anderson E, et al (2002): Reduced hippocampal volume in adult major depression: The role of childhood trauma. *Am J Psychiatry* 159:2072–2080.

Vogt BA, Finch DM, Olson CR (1992): Functional heterogeneity in cingulate cortex: The anterior executive and posterior evaluative regions. *Cereb Cortex* 2:435–443.

Westen D, Ludolph P, Misle B, Ruffins S, Block J (1990): Physical and sexual abuse in adolescent girls with borderline personality disorder. *Am J Orthopsychiatry* 60:55–66.

Zanarini MC (1997): Role of Sexual Abuse in the Etiology of Borderline Personality Disorder. Washington, DC: American Psychiatric Press.

Zanarini MC, Frankenburg FR, Sickel AE, Yong L (1996): *The Diagnostic Interview for DSM-IV Personality Disorders*. Belmont, Massachusetts: McLean Hospital, Laboratory for the Study of Adult Development.

Zanarini MC, Gunderson JG, Marino MF, Schwartz EO, Frankenburg FR (1989): Childhood experiences of borderline patients. *Compr Psychiatry* 30:18–25.