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# Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder

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**Abstract**

Borderline personality disorder (BPD) is a common disorder associated with emotional dysregulation and other symptoms that have been hypothesized to be related to dysfunction of limbic brain areas including hippocampus and amygdala. The purpose of this study was to measure hippocampal and amygdala volumes in BPD. Hippocampal and amygdala volumes were measured with magnetic resonance imaging (MRI) in 10 patients with BPD and 23 control subjects. Patients with BPD had a 21.9% smaller mean amygdala volume and a 13.1% smaller hippocampal volume, compared to controls. These findings are consistent with the hypothesis that alterations in the hippocampus and amygdala are associated with BPD.
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## 1. Introduction

Borderline personality disorder (BPD) is a highly frequent psychiatric disorder affecting 1.3% of the population (Torgersen et al., 2001) that is associated with considerable morbidity. BPD is associated with emotional dysregulation, impulsivity, and self-injurious behavior. Several factors have been hypothesized to lead to BPD including childhood trauma (Zanarini, 1997), invalidating parent–child interactions, and inherited personality styles such as sensation seeking (for a comprehensive review, see Schmahl et al., 2002).

Animal models have been developed that are specific to early stress, including separation of the animal from its mother (Meaney et al., 1988; Plotsky and Meaney, 1993). Preclinical studies found that stress is associated with damage to the

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hippocampus (Sapolsky, 1996; McEwen and Magarinos, 2001). Preclinical studies have also implicated the amygdala in stress and fear responses (Davis, 2001) as well as emotional dysregulation. Based on these findings, we (Schmahl et al., 2002) have hypothesized that alterations in a circuit of brain regions including hippocampus and amygdala underlie symptoms of BPD. Several published studies found reduced hippocampal volume in patients with post-traumatic stress disorder (PTSD) (Bremner et al., 1995; Gurvits et al., 1996; Bremner et al., 1997; Stein et al., 1997) as well as depression in some studies (Sheline et al., 1996; Bremner et al., 2000a; for a comprehensive review, see Bremner, 2002a), while amygdala volumes were found to be enlarged in patients with depression and dysthymia (Tebartz van Elst et al., 1999; Bremner et al., 2000a; Tebartz van Elst et al., 2000).

Few studies have examined brain structure and function in BPD. Earlier neuroimaging studies in BPD did not find ventricular enlargement (Snyder et al., 1983) or changes in ventricle–brain ratio (Lucas et al., 1989). The first published study investigating MRI-based volume of the hippocampus and amygdala (Driessen et al., 2000) found 16% smaller volumes of the hippocampus and 8% smaller volumes of the amygdala in women with BPD compared to healthy controls.

The purpose of the current study was to compare hippocampal and amygdala volume in women with Borderline Personality Disorder and controls. We hypothesized smaller hippocampal and amygdala volumes in patients with BPD.

## 2. Materials and methods

The study group consisted of 10 female patients with BPD and 23 women without BPD. Women were included in the BPD group with current BPD based on the Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV; Zanarini et al., 1996) and a history of childhood sexual and/or physical abuse based on the Early Trauma Inventory, a reliable and valid instrument for the assessment of early trauma (ETI; Bremner et al., 2000b). Ten women in the control group had a trauma history based on the ETI. Subjects were excluded with organic mental disorder, history of head trauma, current alcohol abuse, history of psychotic disorder based on the Structured Clinical Interview for DSM-IV, Axis I (SCID; First et al., 1995), and current use or use in the past 3 months of benzodiazepines. In addition, controls were excluded with a lifetime diagnosis of BPD as assessed by the DIPD-IV, or a current axis I diagnosis assessed by the SCID.

The average age was $27.4 \pm 7.1$ years in the BPD group and $31.5 \pm 8.0$ years in the control group ($P = 0.161$). All 10 patients in the BPD group were right-handed; in the control group three patients were left-handed and 20 were right-handed. One BPD patient was African American, and the other nine were Caucasian; in the control group one subject was Hispanic, five were African American and 17 Caucasian. The control subjects had significantly ($P = 0.004$) more education (17.0 years) than the BPD group (13.9 years). Three of the patients had a past history of alcohol dependence, one had a past history of alcohol abuse, one had a past history of cocaine dependence, one had a past history of cocaine abuse, one had a past history of opioid dependence, one had a past history of polysubstance dependence, one had current laxative dependence, and one had current stimulant abuse. Four patients had a current depressive episode, three had current panic disorder with agoraphobia, one had current panic disorder without agoraphobia, two had current bulimia nervosa, and one had current binge eating disorder. Five of the 10 patients with BPD had a lifetime history of PTSD and three fulfilled criteria for current PTSD. In the control group there were six subjects with past major depressive disorder, two with past PTSD, one with past panic disorder with agoraphobia, one with past OCD, one with past generalized anxiety disorder, one with past mood disorder secondary to a general medical condition, one with past alcohol dependence, one with past cocaine dependence, and one with past cannabis dependence. Nine out of 10 BPD patients and none of the controls were treated with psychotropic medication at the time of the study. After complete explanation of the study, written informed consent was obtained. This study was approved by an IRB.

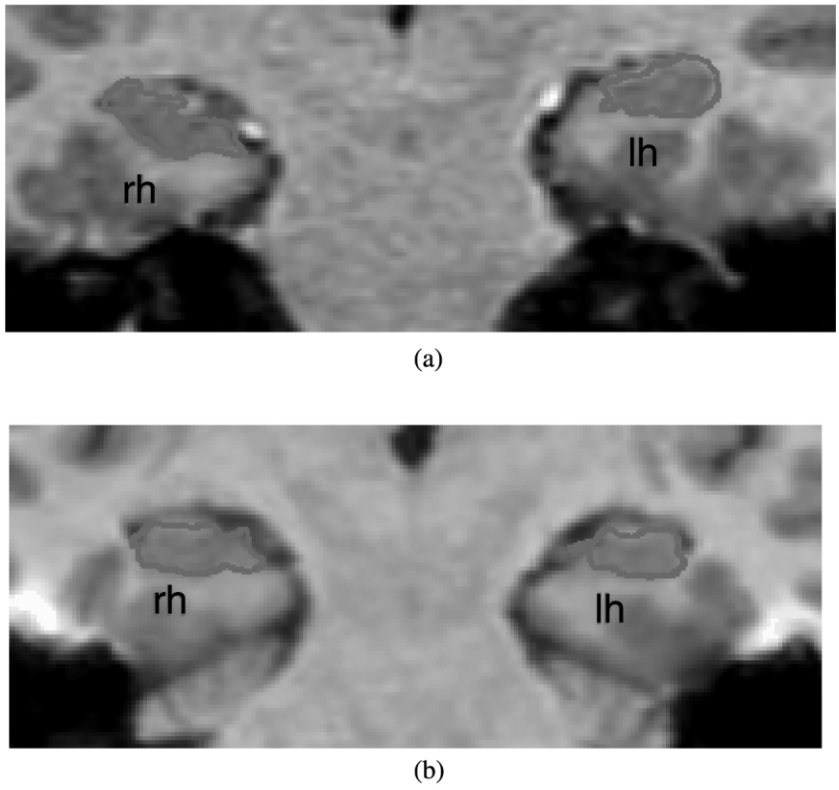


Fig. 1. Hippocampus of a control subject and of a patient with BPD (lh = left hippocampus, rh = right hippocampus): (a) control subject; and (b) patient with BPD.

Magnetic resonance images were obtained using a protocol described in detail elsewhere (Bremner et al., 1995). All measurements were performed by a single trained rater (C.G.S.) without knowledge of the diagnostic group. Accuracy of method was checked with inter-rater reliability. Alpha coefficients for inter-rater reliability were 0.983 for hippocampus and 0.977 for amygdala. Axial images with a slice thickness of 1 mm were reconstructed perpendicular to the longitudinal axis of the hippocampus by a method of reslicing and quadrupling the original MRI data set. Measurement of whole hippocampal volume was performed using ANALYZE (Mayo Clinic, Rochester, MN, USA), drawing hippocampal volume from posterior to anterior in every consecutive slice starting at the slice where the pulvinar of the thalamus interrupts the fornix superiorly and using this as the posterior landmark of the hippocampus. The superior border of the hippocampus was determined conservatively including only gray matter not including the alveus and fimbriae. The inferior border was assessed including the subiculum. A straight line from the inferior subcortical white matter extending medially was used to disconnect the parahippocampal gyrus from the subiculum. Working from posterior to anterior, in several slices around the area displaying the basilar artery, both hippocampus and amygdala were visible, and consequently were both drawn to obtain whole volumes of these brain regions. The uncal recess of the temporal horn of the lateral ventricle was used as the most reliable way to separate the hippocampal head from the amygdala. If the uncal recess was not prominent,

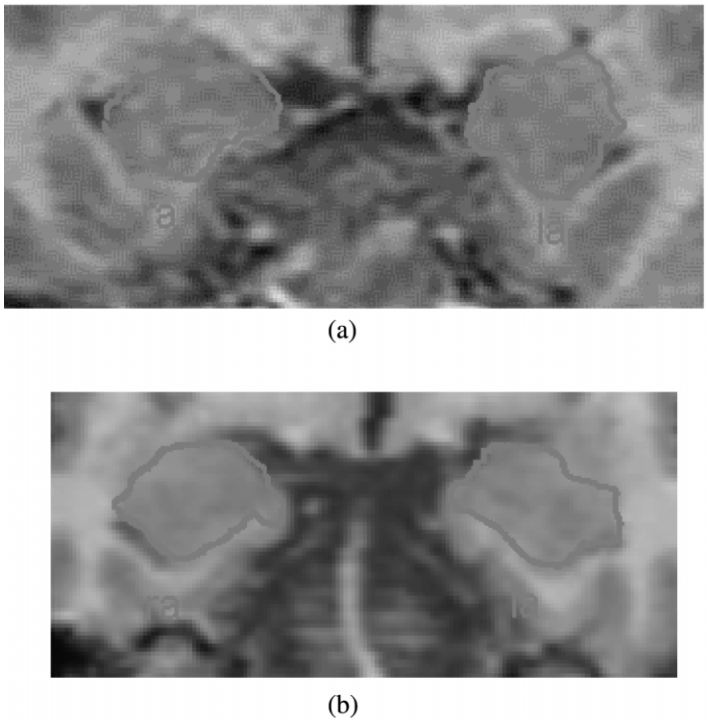

Fig. 2. Amygdala of a control subject and of a patient with BPD (la = left amygdala, ra = right amygdala): (a) control subject; and (b) patient with BPD.

we traced along the alveus or connected the inferior horn of the lateral ventricle to the sulcus at the inferior margin of the semilunar gyrus. The amygdala was also drawn from posterior to anterior starting at the slice where the amygdala was clearly separated from the hippocampus using the method described above, stopping at the last slice where the amygdala was still visualized to distinguish from the surrounding infraorbital gyrus. Whole brain volumes were assessed by tracing the outline of the brain (excluding cerebellum) in all axial slices in which it was visualized.

Repeated measures analyses of covariance (ANCOVAs) with side (L/R) as the repeated measure were used to compare hippocampus and amygdala volumes between groups. Age, years of education, and whole brain volume were added to the model to control for these potentially confounding factors. Significance was defined as $P < 0.05$.

## 3. Results

Repeated measures ANOVA showed a significant main effect for diagnosis ($P = 0.034$), which was related to smaller volumes of the left amygdala ($-23\%$), right amygdala ($-21\%$), left hippocampus ($-11\%$), and right hippocampus ($-16\%$) in BPD patients compared to controls. There was no main effect for side (L/R). These differences were significant when whole brain volume, years of education, and age were added to the analysis. Analysis of individual regions showed that the greatest magnitude of effect was for left and right amygdala (Table 1). See Figs. 1 and 2 for examples of hippocampal and amygdala volumes in patients and controls.

## 4. Discussion

Patients with BPD in this study had smaller volumes of the amygdala ($-21.9\%$) and hippo-

Table 1
Volumes in cubic millimeters ($mm^3$) of the hippocampus and the amygdala in patients with BPD and in controls

| | BPD | | Controls | | Percentage reduction | *P* |
|---|---|---|---|---|---|---|
| | Mean | S.D. | Mean | S.D. | | |
| Left hippocampus | 2120 | 416 | 2380 | 811 | 10.1 | 0.235 |
| Right hippocampus | 1883 | 286 | 2244 | 768 | 16.1 | 0.058 |
| Left amygdala | 1665 | 384 | 2167 | 727 | 23.2 | 0.015 |
| Right amygdala | 1661 | 371 | 2090 | 723 | 20.5 | 0.032 |
| Whole brain | 1 130 573 | 103 580 | 1 216 085 | 101 481 | 7.0 | 0.053 |

campus (−13.1%) compared to controls. These differences were significant controlling for potentially confounding factors of age, whole brain volume, and years of education. Our results confirm the report of Driessen et al. (2000), who found a 16% smaller hippocampal volume and 8% smaller volume of the amygdala.

There are several possible explanations for reduction of hippocampal and amygdala volumes in BPD. BPD is associated with an increase of early life stress and a reduction of hippocampal volume has been associated with stress, the mechanism of which has been hypothesized to be related to increased levels of glucocorticoids, reduced levels of brain-derived neurotrophic factor, inhibition of neurogenesis, or other factors. Patients with BPD respond to a challenge with stressful scripts with higher and longer-lasting cortisol levels compared to controls (Elzinga et al., unpublished results). Thus, repeated exposure to stress, which is one of the main features of BPD, could lead to progressive atrophy of the hippocampus. Smaller hippocampal volume, on the other hand, could predispose to BPD. Smaller amygdala volume could also predispose to BPD. Stress or early life experiences (e.g. parent–child interactions) could lead to changes in the amygdala, the exact mechanism of which, however, is unclear. The amygdala plays a critical role in stress responses and emotion, possibly mediated by corticotropin-releasing hormone (Lombardo et al., 2001). Changes in volume may reflect alterations in synaptic connections or other factors.

Several limitations should be considered when interpreting our findings. First, our sample size was rather small, with 10 patients with BPD and 23 controls. Most of the patients with BPD were taking psychotropic medication. Because of the severity of the disorder, the high level of comorbid depression, and the high risk of suicide in the BPD population, patients without psychotropic medication are difficult to recruit. Besides the high level of comorbid depression, the frequency of comorbid alcohol and drug abuse or dependence is also very high in this disorder. We excluded patients with current alcohol or drug abuse or dependence, respectively, but cannot rule out the possibility that past abuse or dependence influenced our findings of reduced volumes of the hippocampus and amygdala. We also did not exclude patients with depression, so we cannot exclude the possibility that the current findings are related to depression. Five of the 10 patients with BPD had a lifetime history of PTSD and three fulfilled criteria for current PTSD. The small size of the BPD sample, however, did not permit us to divide this group into two subgroups with and without PTSD. However, given the overlap of patients with BPD with other trauma spectrum disorders (Bremner, 2002b), we feel that exclusion of patients with comorbid disorders would lead to a non-representative sample. Future studies should include larger sample sizes and analyze subgroups of patients with different comorbidities.

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