

Smaller stress-sensitive hippocampal subfields in women with borderline personality disorder without posttraumatic stress disorder

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Background: Animal and human studies have suggested that hippocampal subfields are differentially vulnerable to stress, but subfield volume has not been investigated in patients with borderline personality disorder (BPD). Based on the putative role of stressful life events as vulnerability factors for BPD, we hypothesized that patients with BPD would exhibit reduced volumes for the stress-sensitive dentate gyrus (DG) and the cornu ammonis (CA) 3 subfields volumes, and that these volumes would be associated with traumatic childhood experiences. **Methods:** All participants underwent 3 T magnetic resonance imaging. Hippocampal subfield volumes were estimated using an automated and validated segmentation algorithm implemented in FreeSurfer. Age and total subcortical grey matter volume were covariates. We assessed traumatic childhood experiences using the Childhood Trauma Questionnaire (CTQ). **Results:** A total of 18 women with BPD and 21 healthy control women were included in the study. Only 1 patient had comorbid posttraumatic stress disorder (PTSD). The volumes of the left ($p = 0.005$) and right ($p = 0.011$) DG-CA4 and left ($p = 0.007$) and right ($p = 0.005$) CA2–3 subfields were significantly reduced in patients compared with controls. We also found significant group differences for the left ($p = 0.032$) and right ($p = 0.028$) CA1, but not for other hippocampal subfields. No associations were found between CTQ scores and subfield volumes. **Limitations:** The self-reported CTQ might be inferior to more comprehensive assessments of traumatic experiences. The sample size was moderate. **Conclusion:** The volumes of stress-sensitive hippocampal subfields are reduced in women with BPD without PTSD. However, the degree to which childhood trauma is responsible for these changes is unclear.

Introduction

Borderline personality disorder (BPD) is a severe, chronic psychiatric disorder with high morbidity and mortality.¹ The etiology of BPD is far from being elucidated. Childhood traumatization may be important, but its contribution to the development of the disorder has not been clarified.^{1,2}

Several studies^{3–8} and meta-analyses^{9–11} have shown reduced hippocampal volume or grey matter concentration as the most consistent brain structure deviation in people with BPD. Hippocampal volume is influenced by stress exposure in animals and humans,¹² and hippocampal reduction in those with BPD has been linked to traumatization.^{3,4,8} However, several questions regarding the association between traumatization

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and hippocampal structure remain unanswered. For example, a smaller hippocampal volume has been suggested to be a risk factor for psychiatric symptoms,¹³ making the degree to which a general reduction in hippocampal size in individuals with BPD is caused by genetic factors, psychological trauma or other environmental mechanisms difficult to determine. However, animal studies have shown that particular hippocampal subdivisions, including the cornu ammonis (CA) 3 and the dentate gyrus (DG), are prone to morphological changes in response to environmental stressors.¹⁴ Stress also preferentially affects the same regions in humans.^{12,15} Thus, an investigation of these structures may provide important insights into the pathophysiology of BPD.

To the best of our knowledge, hippocampal subfield volumes have not yet been investigated in patients with BPD. This lack of investigation may be related partly to the time-consuming task of manually delineating hippocampal subfields in magnetic resonance imaging data. However, a recently developed automated segmentation procedure yields reproducible measurements that correlate with the manual delineation of hippocampal subfields.¹⁶ A recent study using this method identified an association between childhood trauma and the volumes of the automatically segmented fields containing CA3 and DG (CA2-3 and DG-CA4, respectively) in a community sample.¹²

In the present study, our first aim was to compare hippocampal subfields in women with BPD to those of healthy control women. Because reductions in hippocampal volume have been identified in several major psychiatric disorders,¹⁷⁻¹⁹ we sought to study patients with limited comorbidity to increase the diagnostic specificity of our findings. Based on the putative role of traumatization as a risk factor for BPD and associated reductions in hippocampal size, we hypothesized that the stress-sensitive CA2-3 and DG-CA4 subfields would be smaller in patients than in healthy controls. We expected the volumes of the remaining hippocampal subfields to exhibit less pronounced group differences. Our secondary aim was to investigate whether childhood trauma is associated with the CA2-3 and DG-CA4 volumes. We tested the association between responses to the Childhood Trauma Questionnaire (CTQ) and subfield volumes within the patient group, hypothesizing a negative association between childhood trauma and CA2-3 and DG-CA4 volumes. Finally, in exploratory analyses, we tested the influence of other clinical variables on the volumes of the CA2-3 and DG-CA4 subfields in patients with BPD.

Methods

Participants

The investigations were carried out in 2009 and 2010. We recruited women meeting the DSM-IV criteria for BPD from the Department of Personality Psychiatry at Oslo University Hospital. Axis I and axis II assessments of the patients by psychiatrists specializing in affective disorders (E.B.) and personality disorders (B.H.), respectively, were based on the Mini-International Neuropsychiatric Interview (MINI; version 5.0.0)²⁰ and the

Structured Clinical Interview for Personality Disorders (SCID-II),²¹ respectively. The reliability of the BPD diagnosis was ascertained according to the "Longitudinal, Expert, All Data" (LEAD) principle²² and verified during the course of treatment, which spanned a period of at least 12 months after inclusion in the study. We excluded patients with bipolar spectrum disorder, previous or present psychosis, or schizotypal personality disorder. Special emphasis was placed on the assessment of exclusion criteria for comorbidity, and consensus was reached between B.H. and E.B. for each participant regarding the presence or absence of comorbidities. In cases of doubt, the senior authors S.K. and U.F.M. were consulted concerning axis II and axis I diagnoses, respectively. For the assessment of hypomanic symptoms, patients completed the Hypomania Check-list 32.²³ Patients fulfilling the criteria for current or previous major depressive episodes were asked to estimate their lifetime number of depressive episodes with a minimum duration of 2 weeks. The duration of the episodes was not estimated.

We recruited control women through local advertising. They were of similar age and had similar education levels as the patients. We screened controls for axis I disorders using the MINI and for axis II disorders using the self-reported Personality Disorder Questionnaire version 4 (PDQ-4).²⁴

We obtained demographic and supplementary information for all participants using the Stanley Foundation Network Entry Questionnaire.²⁵ Alcohol and substance use were assessed with the clinical Alcohol Use Scale and Drug Use Scale.²⁶ In addition to the comorbidities already mentioned, we excluded patients if they had a history of hypomanic symptoms lasting more than 1 day. For the control group, the exclusion criteria were any previous or current psychiatric disorder. Additional exclusion criteria pertaining to all participants were previous head injury with loss of consciousness for more than 5 minutes, history of neurologic or other severe chronic somatic disorders, pregnancy and metallic implants.

All participants received an amount equal to approximately \$50 USD for their participation in the study. The Regional Ethical Committee of South-Eastern Norway (REK Sør-Øst) approved our study protocol, and we obtained written informed consent from each participant after providing them with a complete description of the study.

Psychometric assessment

Adverse childhood experiences were assessed using the short version of the CTQ.²⁷ This instrument comprises 25 clinical items assessing 5 different types of childhood trauma: emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. Only total scores, based on weighted scores, were used. We assessed illness severity at the time of scanning using the Borderline Personality Disorder Severity Index (BPDSI).²⁸

Magnetic resonance imaging

Imaging was performed on a 3 T Philips Achieva Scanner (Philips Healthcare) using an 8-channel SENSE head coil. The pulse sequence used for volumetric analysis was a T_1 -weighted

3-dimensional turbo field echo sequence (repetition time 8.4 ms; echo time 2.3 ms; field of view $256 \times 256 \times 220$ mm; 1 mm isotropic resolution; scan time 7 min, 40 s). The sequence was run twice, and we combined the 2 acquisitions during processing to increase the signal-to-noise-ratio.

Volumetric analysis

We estimated hippocampal subfield volumes using a novel segmentation algorithm implemented in FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>).¹⁶ The procedure uses Bayesian inference and a probabilistic atlas of hippocampal formation based on manual delineations.¹⁶ We estimated 8 subfield volumes: DG-CA4, fimbria, CA1, CA2–3, subiculum, presubiculum, hippocampal fissure and an anatomically less specific part of the tail of the hippocampus. We included the DG-CA4, CA1, CA2–3, the fimbria, subiculum and presubiculum in the present analysis (Fig. 1). The subfields correlate well with manual delineations, with correlation coefficients of 0.83 and 0.91 for DG-CA4 and CA2–3, respectively.¹⁶ All segmentations were visually inspected, and no manual corrections were performed. To obtain an approximation of the total hippocampal volume based on this segmentation procedure, the 8 subfield volumes were summed.

We estimated the total subcortical grey matter volume (sGMV) using the standard brain segmentation procedure in FreeSurfer.^{29,30} Similar to previous studies using the same segmentation procedure, sGMV was used as a covariate in the statistical analyses.^{12,31}

Statistical analysis

Statistical analyses were performed using SPSS version 18.0 for Windows. We considered results to be significant at $p < 0.05$, 2-tailed. We calculated the Cohen d statistic to estimate effect size.

To test for group differences in demographic and clinical variables, we used the Student t test and the Fisher exact test for continuous and categorical variables, respectively. We performed analyses of covariance (ANCOVA) to examine group differences in the main analyses of DG-CA4 and CA2–3 subfield volumes and in the exploratory analyses of the fimbria, CA1, subiculum, presubiculum and summed subfield volumes while controlling for age and sGMV. The ANCOVAs for

the subfield volumes were rerun, including handedness and substance use (disorder v. no disorder) as variables to determine whether any significant group effects remained significant when controlling for the potential influence of these factors. To investigate the effects of the CTQ-weighted score on DG-CA4 and CA2–3 subfield volumes, we performed linear multiple regression analyses, covarying for age and sGMV.

In exploratory analyses, the associations between the number of depressive episodes in the patients reporting previous depressive episodes and the DG-CA4 and CA2–3 subfield volumes were investigated using linear multiple regression covarying for age and sGMV. The associations between disorder duration and DG-CA4 and CA2–3 subfield volumes in patients were investigated using linear multiple regression analysis covarying for age and sGMV. We performed ANCOVAs, controlling for age and sGMV, to investigate the effects of medication (medicated vs. nonmedicated) on DG-CA4 and CA2–3 subfield volumes in patients with BPD. Finally, we investigated the associations between BPDSI score and the DG-CA4 and CA2–3 subfield volumes in patients with BPD using linear multiple regression analysis, covarying for age and sGMV.

Results

Participant demographic and clinical data

Eighteen women with BPD and 21 healthy controls were included in the study. Participant age ranged from 18 to 50 years. The demographic and clinical data of participants are summarized in Table 1. There were no significant group differences in age or education level. The patients with BPD had significantly higher weighted CTQ scores than controls. Only 1 patient in our sample had comorbid posttraumatic stress disorder (PTSD). Otherwise the patients presented with varying degrees of childhood traumatization.

DG-CA4 and CA2–3 subfield volumes

Mean subfield volumes adjusted for age and sGMV are provided in Table 2. Patients with BPD had significantly smaller left and right DG-CA4 volumes and left and right CA2–3 volumes than healthy controls. The effect sizes of the reduction

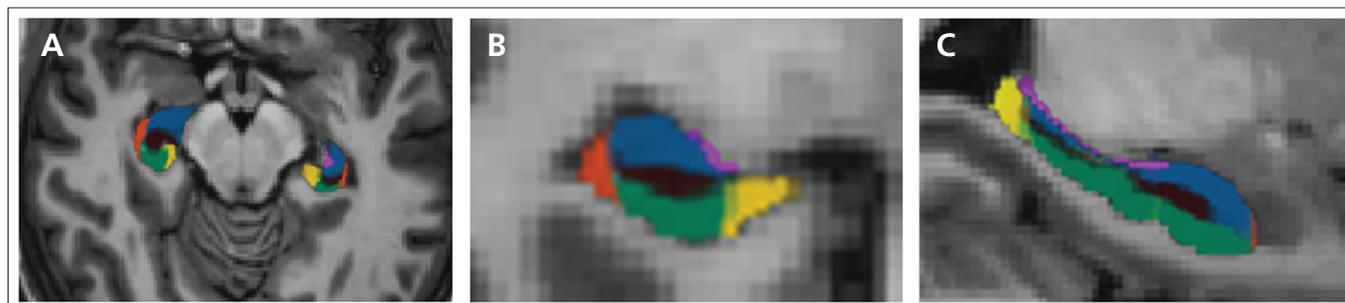


Fig. 1: (A) Horizontal, (B) coronal and (C) sagittal images of hippocampal subfield segmentation in a patient with borderline personality disorder. Dark brown (centre) = DG-CA4; blue = CA2–3; orange = CA1; purple = fimbria; green = subiculum; yellow = presubiculum.

were 1.03 for the left DG-CA4, 0.90 for the right DG-CA4, 1.01 for the left CA2–3 and 1.00 for the right CA2–3.

Controlling for the potential effects of handedness and substance use disorder by including these factors in the ANCOVA, the subfield volumes of the left DG-CA4 ($F = 6.755$, $p = 0.014$), right DG-CA4 ($F = 5.154$, $p = 0.030$), left CA2–3 ($F = 5.421$, $p = 0.026$) and right CA2–3 ($F = 5.997$, $p = 0.020$) remained significantly reduced in the patient group.

CA1, fimbria, presubiculum, subiculum and total volumes

The mean volumes of other hippocampal subfields adjusted for age and sGMV and the subfield sum are provided in Table 2. We found significant group differences in the volumes of the left and right CA1. The effect size of the reduction was 0.82 for both the left and right CA1. No significant group differences were found in the volumes of the fimbria,

presubiculum and subiculum. Significant reductions were also noted in the summed volumes, which are approximations of the total hippocampal volumes.

When we controlled for the potential effects of handedness and the presence of a substance use disorder by including these factors in the ANCOVA, the volumes of the left CA1 ($F = 2.223$, $p = 0.15$) and right CA1 ($F = 2.649$, $p = 0.11$) were no longer significantly reduced in the patient group, whereas the summed volumes exhibited trends toward significant reductions in both the left ($F = 3.900$, $p = 0.06$) and right hemisphere ($F = 3.884$, $p = 0.06$).

Effect of weighted CTQ scores on the DG-CA4 and CA2–3 subfield volumes in patients with BPD

Multiple regression analyses using the left and right DG-CA4 and left and right CA2–3 subfield volumes as dependent

Table 1: Demographic and clinical characteristics of women with borderline personality disorder and healthy controls

Characteristic	Group; no. (%)*		p value
	BPD	Control	
Age, mean \pm SD yr	27.28 \pm 6.31	29.81 \pm 9.62	0.35
Educational level, yr			0.35
0–10	1 (5.6)	0 (0)	
11–13	8 (44.4)	5 (23.8)	
14–17	6 (33.3)	10 (47.6)	
> 17	3 (16.7)	6 (28.6)	
CTQ weighted score, mean \pm SD†	7.27 \pm 5.08	1.24 \pm 1.21	< 0.001
Right-handedness	15 (83.3)	21 (100)	0.09
Age at first disabling symptoms, mean \pm SD yr‡	14.06 \pm 2.65		
Psychotropic medication			
None	11 (61.1)		
Lamotrigine	2 (11.1)		
Antidepressants§	6 (33.3)		
Antipsychotics (olanzapine)	1 (5.6)		
Benzodiazepines	0		
Lithium	0		
Substance use disorder¶	4 (22.2)		
Comorbid personality disorders			
Avoidant and paranoid	2 (11.1)		
Avoidant	4 (22.2)		
Dependent	1 (5.6)		
None	11 (61.1)		
Comorbid axis I disorders, current			
Major depressive episode**	2 (11.1)		
Panic disorder	5 (27.8)		
General anxiety disorder	3 (16.7)		
Social phobia	5 (27.8)		
Posttraumatic stress disorder	1 (5.6)		
No. of depressive episodes \pm SD	18 \pm 14.7		
BPDSI total score \pm SD††	25.9 \pm 8.0		

BPD = borderline personality disorder; BPDSI = Borderline Personality Disorder Severity Index; CTQ = Childhood Trauma Questionnaire; SD = standard deviation.

*Unless otherwise indicated.

†Weighted CTQ score available for 16 patients and 16 controls; range 0.0–16.93 in patients with BPD and 0.0–4.46 in controls.

‡Age at first incidence of disabling symptoms later related to BPD.

§Escitalopram, fluoxetine, bupropion and venlafaxine.

¶Two patients with alcohol abuse, 1 patient with alcohol dependency and 1 patient with benzodiazepine abuse.

**A total of 17 (94.4%) of the patients had experienced at least 1 previous major depressive episode.

††BPDSI score available for 17 patients.

variables and the CTQ score, age and sGMV as independent variables revealed no significant effects of CTQ on the left DG-CA4 ($\beta = 0.246, t = 0.911, p = 0.38; R^2 = 0.172$), right DG-CA4 ($\beta = 0.098, t = 0.355, p = 0.73; R^2 = 0.129$), left CA2-3 ($\beta = 0.242, t = 0.872, p = 0.40; R^2 = 0.120$), or right CA2-3 ($\beta = 0.138, t = 0.505, p = 0.62; R^2 = 0.147$).

Exploratory analyses of clinical variables in patients with BPD

Multiple linear regression analyses using the left and right DG-CA4 and left and right CA2-3 subfield volumes as dependent variables and number of depressive episodes, age, and sGMV as independent variables showed no significant effects of the number of depressive episodes (left DG-CA4: $p = 0.75$, right DG-CA4: $p = 0.16$, left CA2-3: $p = 0.93$, right CA2-3: $p = 0.26$). Multiple linear regression analysis using the left and right DG-CA4 and left and right CA2-3 subfield volumes as dependent variables and disorder duration, age and sGMV as independent variables showed no significant effects of disorder duration (left DG-CA4: $p = 0.57$, right DG-CA4: $p = 0.96$, left CA2-3: $p = 0.66$, right CA2-3: $p = 0.89$).

The ANCOVAs investigating the effect of medication in patients with BPD revealed no significant differences in DG-CA4 and CA2-3 subfield volumes between medicated ($n = 7$) and nonmedicated ($n = 11$) patients (left CA4-DG: $p = 0.81$, right CA4-DG: $p = 0.98$, left CA2-3: $p = 0.95$, right CA2-3: $p > 0.99$) when controlling for age and sGMV. Multiple linear regression analysis using the left and right DG-CA4 and left and right CA2-3 subfield volumes as dependent variables and BPDSI score, age and sGMV as independent variables

showed no significant effects of BPDSI on the right DG-CA4 ($p = 0.13$) or right CA2-3 ($p = 0.16$) subfield volumes. We observed trends toward larger left DG-CA4 ($\beta = 0.469, t = 2.047, p = 0.06; R^2 = 0.329$) and left CA2-3 ($\beta = 0.465, t = 1.952, p = 0.07; R^2 = 0.274$) subfield volumes corresponding to a more severe current BPD state, as measured by the BPDSI score.

Rerunning ANCOVAs to examine group differences in DG-CA4 and CA2-3 subfield volumes without the 1 patient with BPD and comorbid PTSD while controlling for age and sGMV, the subfield volumes of the left DG-CA4 ($F = 8.856, p = 0.005$), right DG-CA4 ($F = 7.537, p = 0.010$), left CA2-3 ($F = 7.952, p = 0.008$) and right CA2-3 ($F = 9.234, p = 0.005$) remained significantly reduced in the patient group.

Discussion

The present study of hippocampal subfield volumes in women with BPD, most of whom did not have comorbid PTSD, had 2 main findings. First, the stress-vulnerable DG-CA4 and CA2-3 subfields were significantly smaller in patients with BPD than in healthy controls. Second, we did not identify any significant association between subfield volumes and reported childhood trauma. To the best of our knowledge, this study is the first to investigate hippocampal subfield volumes in patients with BPD. The reduced volumes in stress-sensitive hippocampal subfields suggest that stress influences hippocampal structure in these patients. However, conclusions regarding such an association cannot be drawn from our findings.

The reduced DG-CA4 and CA2-3 subfield volumes we observed in women with BPD support our hypothesis. The

Table 2: Hippocampal volumes in women with borderline personality disorder and healthy controls

Region	Adjusted mean volumes, mm ³ (SEM)		Group difference, %	ANCOVA*	
	BPD	Control		$F_{1,35}$	p value
DG-CA4					
Left	490 (11)	536 (10)	8.6	9.025	0.005
Right	511 (12)	557 (12)	8.3	7.193	0.011
CA2-3					
Left	880 (22)	966 (20)	8.9	8.150	0.007
Right	921 (24)	1021 (23)	9.8	8.891	0.005
CA1					
Left	290 (8)	314 (7)	7.6	5.002	0.032
Right	297 (9)	325 (8)	8.6	5.248	0.028
Fimbria					
Left	67 (3)	65 (3)	-3.1	0.350	0.56
Right	64 (4)	72 (4)	11.1	1.455	0.24
Subiculum					
Left	575 (12)	600 (11)	4.2	2.155	0.15
Right	566 (16)	585 (15)	3.2	0.816	0.37
Presubiculum					
Left	446 (11)	456 (10)	2.2	0.443	0.51
Right	421 (11)	446 (10)	5.6	2.705	0.11
Sum subfields					
Left	3126 (58)	3339 (54)	6.4	7.021	0.012
Right	3160 (69)	3403 (64)	7.1	6.515	0.015

ANCOVA = analysis of covariance; BPD = borderline personality disorder; CA = cornu ammonis; DG = dentate gyrus; SEM = standard error of the mean.

*Age and subcortical grey matter volume were included as covariates.

magnitudes of the effects were similar for both regions as well as for the left and right hemispheres. We also observed significant bilateral reductions in the volumes of CA1. These reductions did not remain significant when controlling for handedness and substance use disorder. No significant group differences were found in the fimbria, presubiculum and subiculum. Our findings suggest a differential reduction of hippocampal subfield volumes in patients with BPD, with reductions of the volumes belonging to the hippocampus proper (CA1–4) and DG and being most robust in the CA2–3 and DG. Our findings also suggest that reductions in the DG-CA4 and CA2–3 subfield volumes are main contributors to the reductions in total hippocampal volume reported in previous studies of patients with BPD.

In a study using manual demarcations and radial distance mapping, which allows for investigation of differences in shape along the hippocampal surface, Rossi and colleagues³² reported that structural alterations in patients with BPD without PTSD primarily were observed in the subiculum and CA1, which differs from our findings. However, the different methods used in the 2 studies are not directly comparable. Also, the study by Rossi and colleagues included both men and women, and the participants in their study exhibited high rates of alcohol and substance abuse and of antipsychotic, benzodiazepine and mood stabilizing medication use. Together, these factors may explain the divergent findings of the 2 studies.

The DG-CA4 and CA2–3 may be the hippocampal subfields most prone to stress-induced morphological reductions.^{12,14,15} Animal models have shown that chronic stress-induced increases in excitatory amino acid and glucocorticoid levels in the CA3 subfield lead to dendrite remodeling.^{14,33,34} Similarly, in the DG, repeated restraint stress suppresses neurogenesis via glucocorticoid hormones.^{14,35} Human studies supporting these animal findings have emerged in the last few years. A postmortem study found evidence of lasting changes in how the hippocampus is affected by glucocorticoids in suicide completers with a history of childhood abuse.³⁶ Negative associations between childhood trauma and DG-CA4 and CA2–3 subfield volumes have recently been demonstrated in nonclinical populations.¹² Patients with PTSD have reduced DG and CA3 subfield volumes.¹⁵ However, several questions remain regarding the association between stress, trauma and hippocampal structure in humans.

A recent meta-analysis showed that trauma exposure in itself is associated with reductions in hippocampal volume.³⁷ A large community sample study identified associations between childhood maltreatment and left DG-CA4 and CA2–3 subfield volume reductions, and these associations were not mediated by a history of depression or PTSD.¹² Childhood traumatization is probably more common in patients with BPD than in those with other psychiatric disorders^{38,39} and may play a central etiological role in the development of BPD.^{40,41} However, in our patient sample, we failed to identify a negative association between CTQ scores and DG-CA4 and CA2–3 subfield volumes. This negative finding is in line with 2 previous studies of patients with BPD that also failed to identify associations between CTQ scores and hippocampal

reductions.^{7,8} On the other hand, more marked hippocampal reductions in patients with BPD with a history of childhood abuse compared with patients without such a history have been identified,⁴ as have smaller hippocampal volumes in patients with stronger trauma-related symptoms.³ Our negative finding might be due to power issues, but it is also possible that the CTQ fails to capture adverse childhood experiences adequately, at least in the context of their potential impact on brain morphology. For example, the lack of information about the timing of trauma could be important. Notably, the hippocampus may be sensitive to stress in distinctive childhood periods. In a study of sexually abused women, hippocampal volume reductions were associated with abuse at 3–5 years of age.⁴² Another explanation is that separating the effect of one factor, childhood trauma, from other potential influential factors in a complex disorder such as BPD is difficult. Large studies investigating both the whole hippocampus⁴³ and stress-vulnerable hippocampal subfields¹² in non-clinical samples identified negative associations between subfield volumes and CTQ scores. Although speculative, associations between hippocampal volumes and early environmental stressors might be more easily detected in such samples, which have relatively few confounding factors, than in clinical samples where other factors may exert influence on hippocampus morphology and mask true associations between childhood trauma and hippocampal subfield volumes.

Posttraumatic stress disorder is associated with reduced hippocampal volume,⁴⁴ including reductions in the volumes of the DG and CA3.¹⁵ The association between hippocampus morphology and PTSD is of particular interest in the context of BPD. Borderline personality disorder has been proposed as a complicated post-traumatic syndrome,⁴⁰ and though later studies did not support this notion, a comorbid diagnosis of PTSD is more common in patients with BPD than in those with other personality disorders.³⁹ Several studies have attempted to determine the effects of BPD and PTSD on hippocampal volumes, and several meta-analyses of hippocampus morphology and BPD addressed the issue.^{9–11} Although one of these meta-analyses found particularly large reductions of hippocampal volume in patients with BPD and comorbid PTSD,¹⁰ the most recent meta-analysis,¹¹ which included considerably more patients than the 2 previous studies, did not find an association between comorbid PTSD and reductions in hippocampal volume.¹¹ Thus, our results support this most recent finding that BPD is associated with hippocampal reductions regardless of PTSD status.

Most of our participating patients fulfilled the criteria for a previous depressive episode, which is in accordance with the high prevalence of depressive symptomatology in patients with BPD.⁴⁵ A large body of literature supports an association between reduced hippocampal volume and major depressive disorder.¹⁷ Also, a “neurogenesis hypothesis of depression” has been formulated.⁴⁶ The pattern of hippocampal subfield reductions in our BPD sample could thus be associated with their affective symptomatology. However, we did not observe any association between the number of depressive episodes and DG-CA4 and CA2–3 subfield volumes. We cannot exclude the possibility that a more thorough assessment of depressive

burden could have provided different results, but our finding is nevertheless in line with those of the recent meta-analysis by Ruocco and colleagues,¹¹ in which lifetime comorbid depression was unrelated to hippocampal reductions in patients with BPD.

Adults with BPD may have experienced symptoms over a large proportion of their lifetime,⁴⁷ and various factors associated with living with BPD may potentially influence the hippocampus. For example, BPD may be more strongly associated with psychosocial impairment than other psychiatric disorders,⁴⁸ and patients with BPD may perceive stressors as more intense and debilitating than individuals with other psychiatric disorders.⁴⁹ Such factors could conceivably influence hippocampus morphology, as suggested by the results from animal models of chronic social stress.³³ In contrast is our negative finding on the effect of disorder duration on subfield volumes. However, disorder duration may be a too rough an approximation to stress load, and studies obtaining more detailed information about stressors, as well as longitudinal studies, are warranted.

We cannot exclude the possibility that the observed reductions in DG-CA4 and CA2–3 volumes in our study participants may reflect genetically determined risk factors for BPD. Although frequently associated with pathological childhood experiences,⁵⁰ BPD is a disorder with a substantial heritability.⁵¹ In the PTSD literature, twin studies have indicated that small hippocampi might represent a risk factor for the development of the disorder.¹³ Particularly complex interactions between genes and environment may exist in BPD, making the study of hippocampal development especially challenging.^{52,53} Longitudinal and twin studies are needed.

Our study has several strengths. The exclusion of participants with frequently observed comorbidities reduced the potential influence of such disorders. This could be important; for example, in a study of patients with bipolar disorder II using the same subfield assessment, a different pattern of hippocampal alterations with reductions in fimbria volume and less pronounced reductions in the DG-CA4 and CA2–3 subfield volumes was demonstrated.³¹ Furthermore, our results emphasize that the subfield reductions are not related to comorbid PTSD. Finally, the assessment of subfield volumes — in contrast to total hippocampal volumes — adds valuable insight into hippocampus morphology in patients with BPD.

Limitations

The present study has several limitations. First, the sample size was relatively modest, which prevents us from drawing firm conclusions regarding the associations between clinical variables and subfield volumes owing to limited power. Second, the automated subfield segmentation procedure may have limitations, especially in regards to the smaller hippocampus subfields. The correlation between automated and manual segmentation is highest for CA2–3, DG-CA4 and the subiculum and lowest for the fimbria¹⁶ — the smallest subfield assessed in this study. Also, the fimbria volume may be underestimated using automated segmentation.¹⁶ Therefore, although we have no reason to believe that systematic errors are present in the segmentation of one of the groups, the rela-

tive reductions of the different subfields must be interpreted with caution. Third, the use of a self-reported questionnaire to assess childhood trauma may be inferior to a comprehensive interview. Fourth, because only women were included, the generalizability of the volumetric reductions to men with BPD is unknown. Fifth, detailed assessments of the lifetime load of depressive, psychosocial and other stressors were not available, preventing us from drawing firm conclusions regarding the potential influence of these factors. Sixth, several patients were on psychotropic medications, which could potentially influence the results. However, the results of our ANCOVAs suggested that the medication effect is minor. Finally, the cross-sectional study design has inherent limitations regarding causality.

Conclusion

To the best of our knowledge, this study provides the first analysis of hippocampus subfield volume in women with BPD. We found significant volume reductions in the DG-CA4 and CA2–3 subfields, which are particularly vulnerable to stress. However, the lack of an association with the CTQ indicates that traumatic childhood experiences alone are not responsible for these reductions.

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