Reduced Anterior Cingulate and Orbitofrontal Volumes in Child Abuse–Related Complex PTSD

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Objective: Classic posttraumatic stress disorder (PTSD) is associated with smaller hippocampus, amygdala, and anterior cingulate cortex (ACC) volumes. We investigated whether child abuse–related complex PTSD—a severe form of PTSD with affect dysregulation and high comorbidity—showed similar brain volume reductions.

Method: We used voxel-based morphometry to measure gray matter concentrations in referred outpatients with child abuse–related complex PTSD (n = 31) compared to matched healthy nontraumatized controls (n = 28). Complex PTSD was diagnosed using the Structured Clinical Interview for *DSM-IV-TR* and the Structured Clinical Interview for Disorders of Extreme Stress. All respondents were scanned on a 1.5-T magnetic resonance system at the VU Medical Center, Amsterdam, The Netherlands, between September 2005 and February 2006.

Results: As was hypothesized, patients with child abuse–related complex PTSD showed reductions in gray matter concentration in right hippocampus ($P_{SVC\ corrected} = .04$) and right dorsal ACC ($P_{SVC\ corrected} = .02$) compared to controls. In addition, a reduction in gray matter concentration in the right orbitofrontal cortex (OFC) was found. Severity of child abuse and PTSD-hyperarousal correlated negatively with ACC volume. Impulsivity correlated negatively with hippocampus volume, and anger, with hippocampus and OFC volume. Comorbidity of borderline personality disorder—compared to comorbid cluster C personality disorder—accounted for more extensive reductions in the ACC and OFC volume.

Conclusions: In complex PTSD, not only the hippocampus and the ACC but also the OFC seem to be affected, even in the absence of comorbid borderline personality disorder. These results suggest that neural correlates of complex PTSD are more severe than those of classic PTSD.

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Clinical presentation and prognosis of posttraumatic stress disorder (PTSD) are likely to vary with trauma characteristics. Type I traumas—single traumatic events such as a robbery or a natural disaster—are associated with *classic* forms of PTSD: ie, PTSD according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR)* criteria, characterized by symptoms of re-experiencing, numbing, and hyperarousal.[1] Type II traumas—repeated interpersonal traumas such as sexual and physical abuse—are associated with a more severe and chronic form of PTSD. After type II traumas, classic PTSD can be complicated by additional features such as impaired affect regulation (eg, enduring anger, impulsivity, and self-harm), dissociation, disturbances of self-image, somatization, and relational problems.[2–4] This syndrome has been brought under the heading of *PTSD with associated features* in *DSM-IV-TR*[1] or *disorders of extreme stress not otherwise specified* (DESNOS), and it is also known by clinicians as *complex PTSD*. Complex PTSD is associated with worse outcomes[5–8] and high rates of comorbidity, especially with depressive and dissociative disorders, and with borderline personality disorder.[9–11] It tends to run a chronic course in spite of considerable use of medical and psychiatric services.[12] Sexual abuse affects 10% of Dutch and American women.[9,13] The risk of PTSD following exposure to any type of trauma is 10%–20%, with the highest risk associated with assaultive violence.[14] In a student population, prevalence of complex PTSD was found to be 1%.[6]

From a neurobiologic perspective, PTSD is associated with structural and functional changes in limbic structures, in particular the medial temporal lobe (MTL).[15,16] A meta-analysis of 21 structural imaging studies on adults with chronic PTSD[17] revealed a significantly smaller volume of the left amygdala, a region associated with (conditioned) fear responses. In addition, significantly smaller volumes of bilateral hippocampus, a key structure associated with declarative memory, were found. However, a number of magnetic resonance imaging (MRI) studies on PTSD have failed to reveal hippocampal atrophy,[18–21] especially in children,[22] acutely traumatized people,[23] and elderly patients.[24–26] Whether these negative findings are related to methodological issues or reflect pathogenetic differences is as yet unknown.

Whereas most structural MRI studies on PTSD have focused on MTL structures, it should be noted that these regions receive extensive inputs from other cortical areas involved in emotion processing,[27] in particular the prefrontal cortex and the anterior cingulate cortex (ACC). Anterior

cingulate cortex volume was also found to be reduced in PTSD, both with voxel-based morphometry (VBM)[28–32] and region-of-interest (ROI)–based manual segmentation techniques.[31,33,34] Anterior cingulate cortex volume was found to be inversely related to PTSD symptom severity.[32] The ACC is involved in attention as well as in emotion regulation, and it is thought to be critically involved in the pathophysiology of PTSD.[35] The ventral or emotional part of the ACC was found to be hypoactive in PTSD during symptom provocation and cognitive activation paradigms[36] but hyperactive during dissociative states.[37] Hyperactivity was also found in the dorsal part or cognitive division of the ACC during dissociative states and performance of a counting Stroop paradigm.[38] Activity in the ACC and MTL regions was found to be negatively correlated to impulsivity and anger in borderline personality disorder,[39–41] but to our knowledge the relationship between volume and these clinical variables has not yet been investigated.

The above-reviewed volumetric reductions in PTSD have been attributed to both environmental (ie, stress) and genetic factors. Exposure to chronic stress has been shown to damage the hippocampus and the ACC in animal studies with a prospective design[42] and in a human twin study.[30] With regard to hippocampal atrophy in PTSD, the evidence is mixed. On the one hand, successful pharmacotherapy for PTSD was associated with enlargement of the hippocampus,[43] compatible with the stress hypothesis and with neural plasticity. On the other hand, a twin study points at hippocampal atrophy as a genetically determined risk factor to develop PTSD rather than as a result of stress.[44]

Early life stress in particular, during a *window of susceptibility*, may have profound and enduring effects on the regulation of stress later in life. It has been shown that the risk for adult PTSD is higher (eg, in veterans or abused women) if there has been abuse during childhood as well.[45,46] A history of childhood abuse is related to increased neuroendocrine stress reactivity, which is further enhanced when additional trauma is experienced in adulthood.[47] There is also evidence that different brain regions have unique periods of heightened sensitivity to the effects of early stress.[48] The above-mentioned meta-analysis by Karl et al[17] concluded that childhood trauma may have greater impact on (right) hippocampus volume than trauma during adulthood. In a direct comparison of patients with PTSD following prolonged child abuse or after a single trauma during adulthood, however, hippocampus volume did not differ.[49]

In summary, reduced volumes of MTL regions (hippocampus and amygdala) and ACC have been found in classic PTSD. To date, it is unclear whether a similar pattern occurs in child abuse–related or complex PTSD. The main aim of the present study was to investigate if child abuse–related complex PTSD is associated with structural reductions in these brain areas compared to healthy controls and if additional brain areas are involved. In addition, we aimed to explore whether any abnormalities were correlated with PTSD and/or trauma severity, or rather with its complicating symptoms or comorbid psychopathology, such as dissociation, depression, and/ or borderline personality disorder symptoms (eg, impulsivity and anger). To this end, we compared regional gray matter (GM) concentration on a whole-brain voxel by voxel basis in patients with complex PTSD and matched healthy controls, and we performed regression analyses using these clinical variables as covariates. We hypothesized that, in child abuse–related complex PTSD, GM volumes of MTL regions (hippocampus and amygdala) and ACC would be reduced compared to healthy controls.

METHOD

Subjects

Thirty-three female patients with both classic and complex PTSD after childhood sexual and/or physical abuse and 30 healthy nonexposed female controls participated in the study. All patients were recruited by clinical referral to outpatient clinics of 4 Dutch mental health institutes (Amsterdam, Alkmaar, Castricum, and Utrecht). Subjects were interviewed between September 2005 and February 2006 by trained mental health workers with the Structured Trauma Interview (STI).[50] In line with the STI, childhood sexual abuse was defined as repeated, forced sexual contact with a perpetrator in an intimate relationship before the age of 16. Severity of sexual abuse was classified as moderate (touching and groping) or severe (forms of penetration). Physical abuse was defined as repeated maltreatment that could have wounded the child; only moderate (ie, sometimes wounded) to severe forms (frequently wounded, confinement, battering) were included in this study. To assess the presence of classic (ie, according to *DSM-IV-TR* criteria) and complex PTSD, the Clinician Administered PTSD Scale (CAPS)[51,52] and the Structured Clinical Interview for Disorders of Extreme Stress Not Otherwise Specified (SIDES; Van der Kolk BA, Pelcovitz D., Herman JL, et al; 1992, unpublished) were administered. To assess comorbid disorders, the Structured Clinical Interview for *DSM-IV* Axis I disorders (SCID-IV-I)[53] and the Structured Interview for *DSM-IV* Axis II Personality disorders (SIDP-IV)[54] were administered. Symptom severity was measured using the CAPS,[51,52] Beck Depression Inventory (BDI),[55] Dissociative Experiences Scale (DES),[56] Borderline Personality Disorder Severity Index (BPDSI)[57] and Symptom Checklist-90.[58]

Exclusion criteria were antisocial personality disorder; dissociative identity disorder (DID); recurrent psychoses and current alcohol or drug dependence or abuse (ie, not meeting *DSM-IV-TR* criteria for alcohol or drug abuse or dependence during the last month, but respondents were not requested to abstain from all alcohol and/or drug use prior to entry into the study); the use of psychotropic medication other than selective serotonin reuptake inhibitors (SSRIs) in stable dosage for at least a month or low dosage benzodiazepines (maximally 20 mg oxazepam or its equivalent); major neurologic and internal disorders affecting neuroendocrine function; serious head trauma (defined as loss of consciousness for more than 5 minutes); retained metal (eg, pacemaker or surgical clips), and pregnancy. Exclusion of

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DID was based on the amnesia part of the Structured Clinical Interview for Dissociative Disorders,[59] and difficult cases were discussed with a diagnostic expert (N.D.).

Seventy-three patients were screened for participation; of these, 18 were excluded due to the use of tricyclic antidepressants or antipsychotics, 12 refused to participate because of fear of the scanning procedure, 5 had a history of serious head trauma, 2 were too obese to lie comfortably in the scanner, 2 had metal implants, and 1 had a major internal disease.

Female controls matched for age were recruited via advertisements in local newspapers. The Medical Ethical Committee of the VU University Medical Center, Amsterdam, The Netherlands, approved the present study. Written informed consent was obtained from each participant.

MRI Acquisition

Structural magnetic resonance (MR) imaging was performed on a 1.5-T Sonata MR system (Siemens, Erlangen, Germany), equipped with a standard head coil, at the VU University Medical Center. To reduce motion artifacts, the subject's head was immobilized using foam pads. A coronal 3D gradient-echo T1-weighted MR image (flip angle = 8°; TR = 2700 ms; TE = 4 ms; TI = 950 ms; BW = 190 Hz/pixel, matrix = 256 × 256, voxel size = 1 × 1 × 1.5 mm, 160 slices) was performed. All patients and controls were scanned on the same scanner using identical imaging parameters. A trained radiologist evaluated MRI scans, and there were no substantial abnormalities in any of the patients or controls. All respondents also participated in a functional MRI study, the results of which will be reported elsewhere.

MRI Data Processing

Image preprocessing was performed using statistical parametric mapping (SPM5) software (Wellcome Trust Centre for Neuroimaging, London, United Kingdom: www.fil.ion.ucl.ac.uk/spm), running in MATrix LABoratory 7.0 (MathWorks, Natick, Massachusetts). DICOM images were converted to Analyze format, followed by manual reorienting to the anterior commissure. Voxel-based morphometry involves a voxelwise comparison of the local concentration of GM between 2 groups of subjects. To this end, the images were segmented (in native space) into GM, white matter (WM), and cerebrospinal fluid probability maps using SPM5 default priors. The segmentation step also comprised a correction for image density nonuniformity to correct for density variations due to position differences of various brain structures within the MRI head coil. GM and WM images were then normalized to anatomic standard space as defined by the MNI-152 template available in SPM5 and resampled to 2 mm isotropic voxels. During normalization, a modulation step was included using the Jacobian determinants of the transformation to account for resulting volume changes. These modulated GM/WM maps were smoothed with an 8 mm full-width half-maximum Gaussian kernel to correct for remaining between-subject registration differences and to render the data more normally distributed, increasing the validity of parametric statistical tests. Because of the small size of the hippocampus, a 4 mm smoothing kernel was used for this structure, as has been recommended.[30]

Gray or white matter concentration is equivalent to the weighted average of the gray or white matter voxels located in

Table 1. Demographic Variables of Patients With Complex PTSD[a] (n = 33) and Healthy Controls (n = 30) (all female)

Variable	Patients With Complex PTSD (n = 33)	Healthy Controls (n = 30)
Age, mean (SD), y	35.3 (9.8)	35.2 (12.3)
Years of education, mean (SD)	10.8 (2.5)[b]	11.4 (2.0)[b]
Right-handed, n (%)	32 (97)	28 (93)

[a]After childhood sexual and/or physical abuse.
[b]Controls > patients; Mann-Whitney test: Z = −2.1, *P* = .033.
Abbreviation: PTSD = posttraumatic stress disorder.

Table 2. Clinical Status Variables of Included Complex PTSD Patients (n = 33)[a]

Variable	Complex PTSD Patients (n = 33)
Childhood trauma, n (%)	
Both physical and sexual	19 (58)
Sexual abuse	11 (33)
Physical abuse	3 (9)
Adulthood trauma, n (%)	
Both physical and sexual	10 (30)
Sexual abuse	10 (30)
Physical abuse	4 (12)
No. of current comorbid Axis I diagnoses (*DSM-IV-TR*), mean (SD)	2.7 (1.8)
Other anxiety disorders,[b] n (%)	23 (70)
Major depressive disorder, n (%)	21 (64)
Eating disorders,[c] n (%)	3 (9)
Other mood disorder,[d] n (%)	3 (9)
Alcohol dependence, n (%)	1 (3)
"Highly dissociative" (DES score > 35), n (%)	9 (27)
No. of Axis II diagnoses (*DSM-IV-TR*), mean (SD)	0.9 (0.8)
Borderline personality disorder, n (%)	11 (33)
Cluster-C personality disorder, n (%)	10 (30)
Both borderline and cluster-C personality disorders, n (%)	3 (9)
Symptom severity, mean (SD)	
CAPS score[e]	88.5 (15.0)
BDI score[f]	29.3 (10.0)
DES score[g]	23.9 (14.5)
BPDSI score[h]	22.9 (7.9)
SCL-90 score[i]	273.9 (49.2)

[a]All patients fulfilled criteria for both "classic" PTSD (according to *DSM-IV-TR*; SCID-I) and complex PTSD (SIDES).
[b]Social phobia, panic disorder, specific phobia, generalized anxiety disorder, obsessive-compulsive disorder.
[c]Anorexia or bulimia nervosa, binge eating.
[d]Dysthymia, bipolar II disorder.
[e]CAPS range, 0–136; score > 40 = indicative for PTSD.
[f]BDI range, 0–63; score > 30 = indicative for severe depression.
[g]DES range, 0–100; score > 35 = highly dissociative, indicative for dissociative disorder NOS.
[h]BPDSI range, 0–90; score > 15 = indicative for borderline personality disorder.
[i]SCL-90 range, 90–450.
Abbreviations: BDI = Beck Depression Inventory, BPDSI = Borderline Personality Disorder Severity Index, CAPS = Clinician Administered PTSD Scale, DES = Dissociative Experiences Scale, NOS = not otherwise specified, PTSD = posttraumatic stress disorder, SCID-I = Structured Clinical Interview for *DSM-IV* Axis I disorders, SCL-90 = Symptom Checklist-90, SIDES = Structured Clinical Interview for Disorders of Extreme Stress NOS.

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Table 3. Brain Regions (Brodmann area and MNI-coordinates for peak intensity) With Reduced Gray Matter Density in Complex PTSD Patients (n = 31) Compared to Healthy Nonexposed Controls (n = 28)

Brain Region	x, y, z (mm)	k	z	$P_{SVC\ Corrected}$	$P_{Uncorrected}$
Left SMA, medial frontal gyrus (BA 6)	−10, −4, 66	43	4.33	…	.0000075
Left SMA, medial frontal gyrus (BA 6)	−12, −26, 62	19	3.63	…	.00014
Right SMA, medial frontal gyrus (BA 6)	12, 0, 60	10	3.61	…	.00015
Right dorsal ACC[a] (BA 9)	**8, 30, 32**	**36**	**3.92**	**.015**	**.000044**
Right OFC (BA 11)	6, 18, −20	27	3.84	…	.000062
Right DLPFC (BA 10)	24, 46, 18	13	3.31	…	.00046
Right hippocampus[a,b]	**34, −6, −26**	**5**	**3.37**	**.037**	**.00037**

[a]A priori predicted areas were reported at a small volume corrected $P < .05$; other areas were reported at an uncorrected $P < .001$; height threshold T = 3.24; extent threshold k ≥ 10 voxels.
[b]Smoothed with a 4 mm FWHM Gaussian kernel; all other areas with 8 mm.
Abbreviations: ACC = anterior cingulate cortex, BA = Brodmann area, DLPFC = dorsolateral prefrontal cortex, FWHM = full width at half maximum, MNI = Montreal Neurological Institute, OFC = orbitofrontal cortex, PTSD = posttraumatic stress disorder, SMA = supplementary motor area, SVC = small volume correction.

the volume defined by the smoothing kernel, and according to previous studies, the regional gray or white matter concentration can be considered to represent the local amount of gray or white matter.[60,61]

Statistical Analysis

Demographic data were analyzed using a Mann-Whitney test (since age and educational years were not normally distributed) and a χ^2 test (for handedness).

Statistical parametric mapping software was employed to assess regional differences in GM/WM density between patients and controls, using analysis of covariance with total GM/WM volume as a covariate. In addition, regression analyses were performed to investigate the correlation between WM/GM changes and trauma/symptom severity, using the STI, CAPS, BDI, DES, and BPDSI. For our a priori ROIs, we adopted a threshold of $P < .05$ corrected for multiple comparisons with an extent threshold of 5 voxels, employing the small volume correction option implemented in SPM5 of 3.5 mL for the hippocampus (each side) and 10 mL for bilateral dorsal ACC, similar to previous research.[30] For exploratory purposes, other regional group differences and results of regression analyses are reported at a threshold of $P < .001$ uncorrected with an additional extent threshold of 10 voxels.

RESULTS

Subjects

One patient panicked during the scanning session; in addition, the structural MRI scans of 1 patient and 2 controls had to be discarded due to technical problems, leaving 31 patients and 28 controls for MRI data analysis. Matching variables of both groups are listed in Table 1. All subjects were female by inclusion. Controls matched well with regard to age and handedness. Education years in patients were lower compared to control subjects, but this difference, although statistically significant, was presumably not meaningful (10.8 vs 11.4 years).

In Table 2, clinical status variables are shown. All patients had suffered repeated trauma of moderate to severe intensity before the age of 16: 58% of patients had experienced both physical and sexual abuse, 33% only sexual abuse, and 9% only physical abuse during childhood. Furthermore, it was found that 73% of patients had also been abused as adults. Controls had experienced no sexual or physical abuse or other major psychotraumatic experiences.

All patients met criteria for PTSD (CAPS) and for complex PTSD (SIDES) by inclusion. Patients had a mean of 2.7 (SD = 1.8) Axis I diagnoses (*DSM-IV-TR*), mostly depressive and anxiety disorders. One respondent was found to have alcohol-dependence later during the course of the study. We decided not to exclude her. Patients had a mean of 0.9 (SD = 0.8) Axis II diagnoses (*DSM-IV-TR*), mainly borderline and cluster C personality disorders.

Symptom ratings from our patients were indicative of severe PTSD (mean CAPS score: 88.5, SD = 15.0; cutoff score = 40, indicating PTSD) and severe depression (BDI: 29.3, SD = 10.0; cutoff for severe depression = 30), as well as moderate-to-severe dissociation (DES: 23.9, SD = 14.5), and borderline pathology (BPDSI: 22.9, SD = 7.9; > 15 indicative of borderline personality disorder). Nine patients (27%) had a score higher than 35 on the DES, which is indicative of dissociative disorder NOS.[62,63]

Medication use in our patient group was restricted to SSRIs in a stable dosage for at least 1 month before entering the study (21 subjects, ie, 64%; mean fluoxetine-equivalent dose = 35.7 mg, SD = 18.6) and/or benzodiazepines in low dosage (16 subjects, ie, 48%; mean oxazepam equivalent = 11.9 mg, SD = 4.0).

GM Concentrations

Results for group comparisons with regard to regional GM volume differences are listed in Table 3. In patients, GM concentration was reduced in the right dorsal anterior cingulate cortex (ACC) and right hippocampus relative to healthy controls (Figure 1). In addition, patients showed smaller GM concentrations in the right orbitofrontal cortex (OFC), in the right dorsolateral prefrontal cortex (DLPFC) and right supplementary motor area (SMA). We did not find regions in which GM concentration was increased in patients relative to controls, nor did we observe WM differences between groups.

Additional multiple regression analyses (Table 4) revealed a negative correlation between dorsal ACC volume and (1) severity of child abuse and (2) the hyperarousal cluster of the CAPS within the group of patients with complex PTSD. Other clusters of the CAPS (re-experiencing and avoidance), BDI (severity of depression), DES (severity of dissociation) or BPDSI were not correlated with ACC volume. Child abuse and impulsivity—as measured by the BPDSI—were inversely correlated with hippocampus volume. Furthermore, anger (BPDSI)—as is illustrated in Figure 2—was negatively correlated with the volume of the OFC extending into the medial

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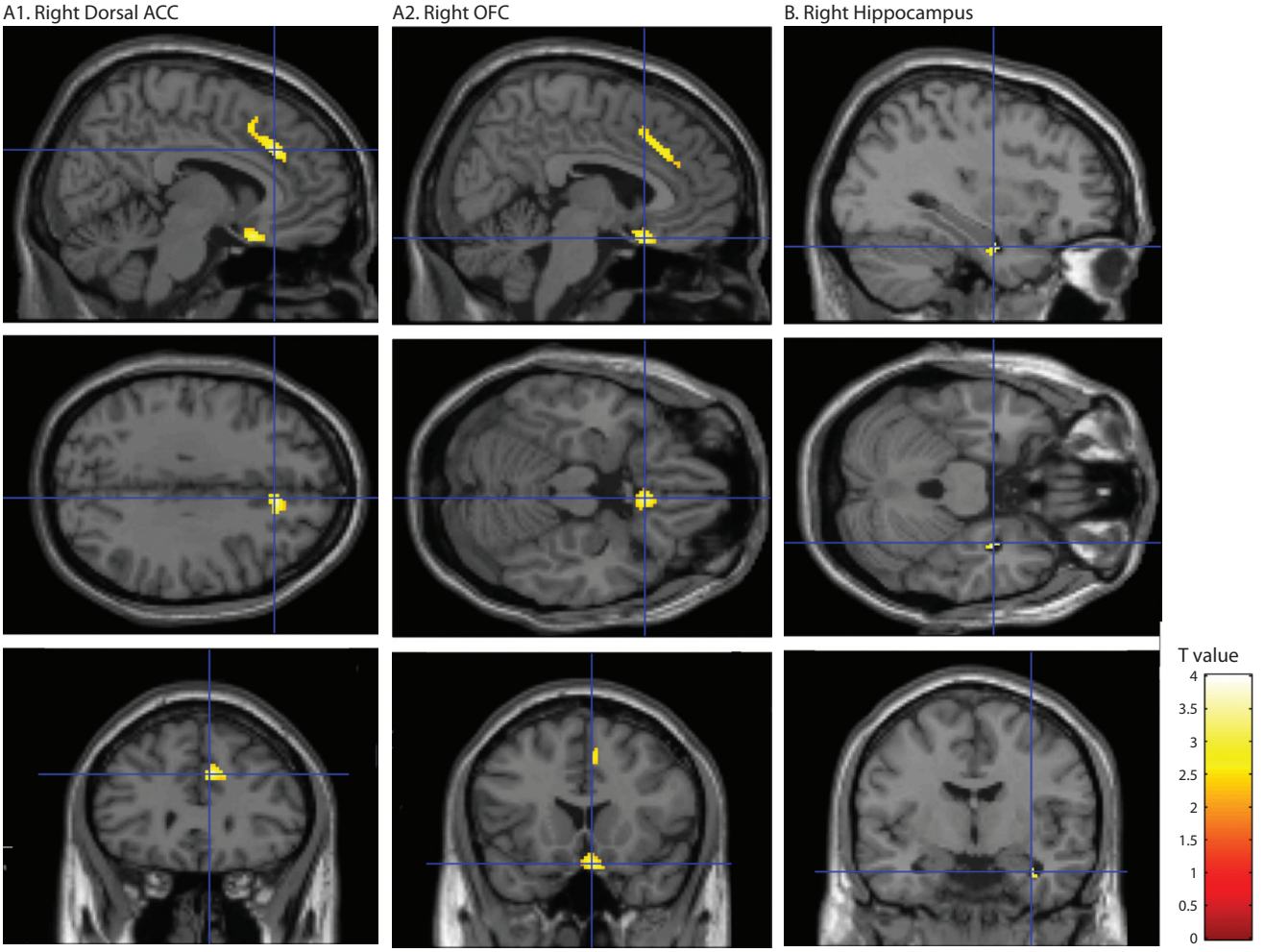
Figure 1. Brain Regions Showing Reduction of Gray Matter Concentrations in Patients With Complex PTSD (n = 31) Compared to Healthy Nontraumatized Controls (n = 28)[a]



[a]Statistical parametric mapping (SPM) with a smoothing Gaussian kernel filter of 8 mm revealed smaller gray matter concentrations in (A1) the right dorsal anterior cingulate cortex (ACC; peak at 8, 30, 32) and (A2) right orbitofrontal cortex (OFC; peak at 6, 18, −20). SPM with a smoothing Gaussian kernel filter of 4 mm revealed a reduction of gray matter concentrations in (B) the right hippocampus (peak at 34, −6, −26). Images created at $P < .005$ uncorrected with extent threshold of 90 resp. 30 voxels for illustrative purposes.
Abbreviation: PTSD = posttraumatic stress disorder.

temporal lobe. No other clinical variables were correlated with hippocampus or OFC volume.

Post hoc analyses revealed that patients with both complex PTSD and borderline personality disorder (n = 10) showed smaller GM concentrations in the dorsal ACC (peak at 8, 52, 4; k = 30, z = 3.58, $P < .001$) and in the OFC (peak at 0, 14, −24; k = 26, z = 3.53, $P < .001$) than patients with complex PTSD and a cluster C personality disorder (n = 10). Comparing complex PTSD patients with comorbid major depressive disorder (MDD; n = 20) to non-MDD complex PTSD patients (n = 11) did not reveal significant GM differences.

DISCUSSION

In the present VBM study, complex PTSD patients (n = 31) were found to have reduced GM concentrations in the right hippocampus, right ACC, and OFC, compared to nontraumatized controls (n = 28). Moreover, severity of impulsivity was negatively correlated with hippocampus volume, and severity of anger with the volume of the OFC extending into the medial temporal lobe.

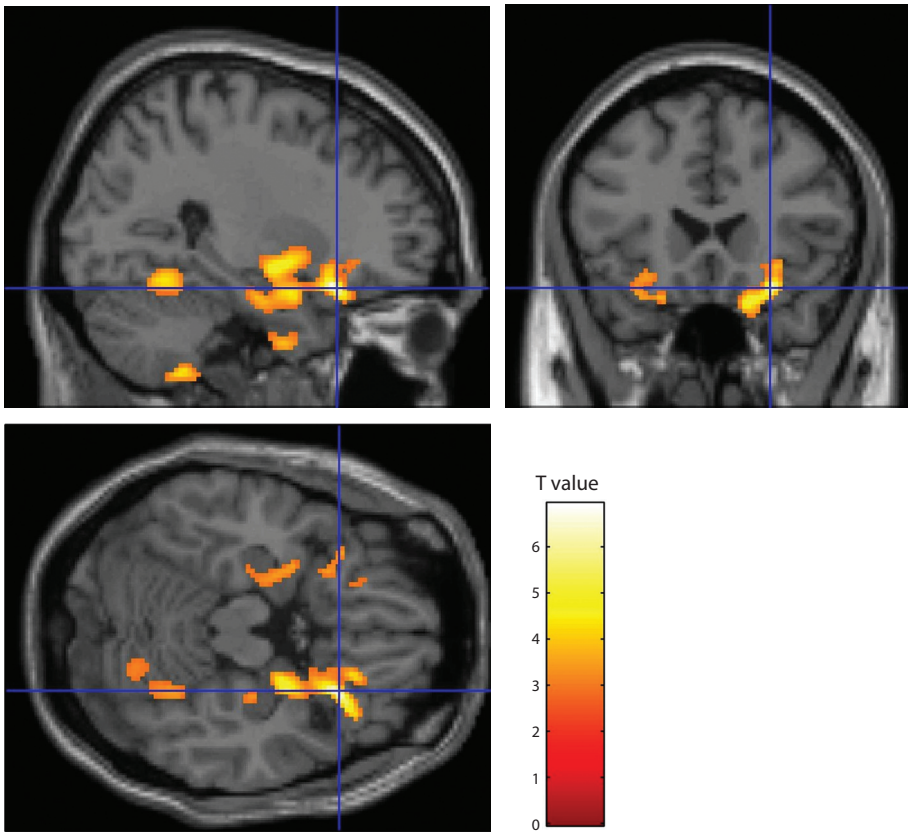
Reduced hippocampal volume is consistent with the extensive literature on hippocampal atrophy in "classic" PTSD,[17] as is the reduced ACC volume, although this latter finding has been less often replicated.[28–34] To our knowledge, this is the first study that replicates this finding in child abuse–related complex PTSD. In previous studies on child abuse–related PTSD,[49,64–66] that also reported hippocampal volume loss, complex PTSD and Axis II comorbidity were not assessed, so that the results are difficult to compare. In our patients, dorsal ACC volume correlated inversely with severity of the PTSD hyperarousal cluster and trauma severity, while in other studies on PTSD, a negative correlation has been found between ACC volume and the re-experiencing cluster[30] and total score of CAPS.[32]

Table 4. Multiple Regression: Negative Correlations of the Severity of Child Abuse, Severity of PTSD Hyperarousal (CAPS), and Severity of Impulsivity and Anger (BPDSI) With Brain Regions With Reduced Gray Matter Density in Patients With Complex PTSD (n = 31)

Variable	Brain Region	x, y, z (mm)	k	z	$P_{SVC\ Corrected}$	$P_{Uncorrected}$
Child abuse	Left SMA	−10, 4, 64	27	4.04	…	.000027
	Right SMA	12, 8, 60	14	3.70	…	.00011
	Right dorsal ACC[a]	10, 26, 28	48	3.95	.0068	.000039
	Right OFC	…	…	…	…	…
	Right hippocampus[a,b]	30, −30, −10	7	3.34	.019	.00042
Hyperarousal (CAPS)	Left SMA	−18, −14, 56	28	4.16	…	.000016
	Right SMA	8, −2, 62	26	4.38	…	.0000059
	Right dorsal ACC[a]	14, 36, 16	61	3.83	.0038	.000063
	Right OFC	…	…	…	…	…
	Right hippocampus[a,b]	…	…	…	…	…
Impulsivity (BPDSI)	Left SMA	…	…	…	…	…
	Right SMA	…	…	…	…	…
	Right dorsal ACC[a]	…	…	…	…	…
	Right OFC	…	…	…	…	…
	Right hippocampus[a,b]	30, −14, −16	18	4.21	.0015	.000013
Anger (BPDSI)	Left SMA	…	…	…	…	…
	Right SMA	…	…	…	…	…
	Right dorsal ACC[a]	…	…	…	…	…
	Right OFC	28, 22, −18	348	5.23	…	.000000084
	Right hippocampus[a,b]	24, −6, −14	395	4.87	.000000016	.00000055

[a]A priori predicted areas were reported at a small volume corrected $P < .05$; other areas were reported at an uncorrected $P < .001$, height threshold T = 3.24; extent threshold k ≥ 10 voxels.
[b]Smoothed with a 4 mm FWHM Gaussian kernel; all other areas with 8 mm.
Abbreviations: ACC = anterior cingulate cortex, BPDSI = Borderline Personality Disorder Severity Index, CAPS = Clinician Administered PTSD Scale, OFC = orbitofrontal cortex, PTSD = posttraumatic stress disorder, SMA = supplementary motor area, SVC = small volume correction.

Figure 2. Negative Correlation of the Severity of Anger (measured by the BPDSI) With Gray Matter Concentrations in the Orbitofrontal Cortex (peak at 28, 22, −18) Extending Into the Medial Temporal Lobe (peak at 24, −6, −14) in Complex PTSD Patients (n = 31)[a]



[a]Image created at $P < .005$ uncorrected with extent threshold of 90 voxels for illustrative purposes.
Abbreviations: BPDSI = Borderline Personality Disorder Severity Index, PTSD = posttraumatic stress disorder.

In contrast, our finding of reduced right OFC volume in complex PTSD patients has been observed only once in classic PTSD (in cancer survivors)[67] and in MDD,[68] but appears to be in line with imaging studies in borderline personality disorder patients[69,70] that have shown both structural,[69,70] and functional[41,71] OFC abnormalities. The OFC is thought to be involved in the extinction of conditioned fear, emotion regulation, and the retrieval of emotional memory,[67,72] and it is associated with impulsivity.[41]

Finally, patients showed a smaller GM volume of the right DLPFC and bilateral SMA, areas that are involved in executive functions, for example (verbal) working memory.[73] To our knowledge, smaller volumes of these areas have not been found in PTSD before, although abnormal functioning of the DLPFC has been found in PTSD (both hypoactivity[74] and hyperactivity[75]) and in dissociative disorder (hyperactivity).[76]

In the present study, impulsivity ratings were negatively correlated with hippocampus volume, and anger ratings were negatively correlated with OFC volume extending into the MTL. Both impulsivity and anger are clinically relevant symptoms of complex PTSD, and they are characteristic for borderline personality disorder as well. Treatment outcome in PTSD patients has been found to be negatively affected by anger severity.[77–80] In the long term, symptoms of impulsivity (eg, self-mutilation and suicide efforts) tend to resolve more quickly than affective symptoms (eg, anger), which may represent more enduring aspects of the disorder.[81] The presence of comorbid borderline personality disorder is likely to require more structured treatments,[82,83] but not all complex

PTSD patients meet criteria for borderline personality disorder. It has been suggested that complex PTSD contains an externalizing subgroup (with predominantly anger and impulsivity, eg, aggression toward others or self-injurious behavior as in borderline personality disorder) and an internalizing subgroup (with predominantly subassertiveness and avoidance).[84] A post hoc analysis on our data revealed that patients with both complex PTSD and borderline personality disorder showed smaller GM concentrations in the dorsal ACC and OFC than patients with complex PTSD and a cluster C personality disorder, implying that the externalizing subgroup had more severe abnormalities than the internalizing subgroup. These results should be interpreted with care, however, because of the small sample size of this post hoc analysis.

Regional brain volume reductions, as observed in the present study, are presumably not specific for PTSD. Major depressive disorder has been reported to be associated with a smaller hippocampal volume as well, especially after multiple episodes.[85] Interestingly, however, a comparison of MDD patients with early childhood abuse versus nontraumatized MDD patients revealed hippocampal volume loss in the trauma-exposed group only.[86] Furthermore, hippocampal volume was found to be reduced in patients with DID,[87,88] but not in DID without comorbid PTSD,[89] and in borderline personality disorder.[90–93] Moreover, severity of the experienced trauma was negatively correlated with hippocampal volume. Reduced ACC volume has similarly been found in MDD but only after 3 or more episodes[94] and in borderline personality disorder.[70,95] Thus, volume loss in the hippocampus and ACC may not be specific for PTSD but may be a feature of psychiatric disorders related to (complex) trauma.

In the present study, depression and dissociation severity were not correlated with ACC, OFC, and hippocampus volumes. Furthermore, a post hoc analysis revealed that the presence of comorbid MDD could not account for volume differences observed in our complex PTSD group. In addition, we failed to observe amygdala atrophy in our complex PTSD patients, as has been found in classic PTSD and also in MDD,[96] borderline personality disorder,[97,98] and DID.[87,88] The role of comorbid depression with regard to amygdala volume is not yet clear, in view of the fact that another study reported *larger* amygdala volumes in borderline personality disorder patients with comorbid MDD compared to borderline personality disorder without MDD.[99]

Our study has both strengths and limitations. The sample size in the present study (31 complex PTSD subjects and 28 controls) is fairly high for VBM studies, while the clinical heterogeneity of our population—inherent to complex PTSD—can be considered a strength as well as a limitation of the present study. Consequently, although we excluded current alcohol or drug dependence or abuse, we did not request subjects to refrain from alcohol or drug use prior to entry into the study. Another potential limitation is the use of SSRIs, which we decided to allow based on considerations regarding feasibility and generalizability. Although long-term SSRI treatment has been associated with increased hippocampal volume,[43] those results should be considered preliminary since they were part of an open, uncontrolled study, and to our knowledge replications have not yet been published. Moreover, if SSRI use may result in increased hippocampal volume, this possibility cannot explain our findings of *decreased* MTL volume in the complex PTSD group. Furthermore, although VBM is an objective and comprehensive assessment of regional anatomic differences throughout the brain,[60,61] it has its limitations as well. False-positive or false-negative VBM findings cannot be completely ruled out, especially with regard to the detection of structural changes in very small brain regions.[100] Additionally, VBM may be biased against finding group differences in areas that are spatially complex.[101] And finally, we cannot rule out the possibility that the abnormalities detected by VBM in our study reflected group differences in the shape of brain structures rather than their volume.[29]

In conclusion, we investigated structural brain abnormalities in child abuse–related complex PTSD, characterized by severe PTSD symptoms, severe affect dysregulation, and severe comorbidity on *DSM-IV* Axis I and II. On the one hand, decreased ACC and hippocampal volume in child abuse–related complex PTSD was found to be similar to findings in the literature regarding other forms of PTSD. On the other hand, our finding of reduced OFC volume associated with impulsivity and anger ratings are more in agreement with studies in patients with borderline personality disorder, although only about a third of our complex PTSD patients fulfilled criteria for borderline personality disorder, and complex PTSD patients without comorbid borderline personality disorder showed smaller OFC volumes as well. Furthermore, these correlates have been found in other trauma-related disorders, suggesting that these correlates are not disorder specific but trauma specific. Although we did not compare classic and complex PTSD directly, these results suggest that complex PTSD is likely to be considered a worse and indeed more complex neural condition than classic PTSD.

Drug name: fluoxetine (Prozac and others).

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