Brain Structures in Pediatric Maltreatment-Related Posttraumatic Stress Disorder: A Sociodemographically Matched Study

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Background: *Previous investigations suggest that maltreated children evidence alterations of chemical mediators of stress and adverse brain development. Previous anatomical magnetic resonance imaging (MRI) brain studies have not controlled for socioeconomic status.*

Methods: *In this study, 28 psychotropic naïve children and adolescents with maltreatment-related posttraumatic stress disorder (PTSD) and 66 sociodemographically similar healthy control subjects underwent comprehensive clinical assessments and anatomical MRI brain scans.*

Results: *Compared with control subjects, subjects with PTSD had smaller intracranial, cerebral, and prefrontal cortex, prefrontal cortical white matter, and right temporal lobe volumes and areas of the corpus callosum and its subregions (2, 4, 5, 6, and 7), and larger frontal lobe cerebrospinal fluid (CSF) volumes than control subjects. The total midsagittal area of corpus callosum and middle and posterior regions remained smaller in subjects with PTSD, whereas right, left, and total lateral ventricles and frontal lobe CSF were proportionally larger than in control subjects, after adjustment for cerebral volume. Brain volumes positively correlated with age of onset of PTSD trauma and negatively correlated with duration of abuse. Significant gender × group effect demonstrated greater lateral ventricular volume increases in maltreated male subjects with PTSD than maltreated female subjects with PTSD. No hippocampal differences were seen.*

Conclusions: *These data provide further evidence to suggest that maltreatment-related PTSD is associated with adverse brain development. These data also suggest that male children may be more vulnerable to these effects.*

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Introduction

Child maltreatment, defined as neglect, physical abuse, sexual abuse, and emotional maltreatment, is a common contributor to child and adult mental illness in this country (Felitti et al 1998). Posttraumatic stress disorder (PTSD) is commonly seen in maltreated children, especially during the period immediately following maltreatment disclosure (Famularo et al 1993, 1996; McLeer et al 1998). Furthermore, partial PTSD responses are commonly seen in victims of childhood maltreatment (Armsworth and Holaday 1993; Famularo et al 1994; Hillary and Schare 1993; Mannarino et al 1994; Wolfe and Charney 1991; Wolfe et al 1994). These partial symptoms may also contribute to substantial functional impairment and distress (Carrion et al 2001b).

Although limited, the psychobiological data in maltreated children suggest that maltreated children and adolescents with mood and anxiety symptoms (i.e., PTSD symptoms) show evidence of altered catecholamines and hypothalamic–pituitary–adrenal (HPA) axis activity. These include findings of greater 24-hour urinary norepinephrine concentrations in neglected depressed male subjects (Queiroz et al 1991) and greater 24-hour urinary catecholamine and catecholamine metabolite concentrations in dysthymic, sexually abused girls (De Bellis et al 1994b). Results from pediatric studies suggest that maltreated children show evidence of corticotrophin-releasing hormone or factor hypersecretion. These include findings of hypersecretion of morning cortisol in sexually abused girls (Putnam et al 1991) and dysregulation of the HPA axis in depressed, maltreated children (Hart et al 1996;

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Kaufman et al 1997b) and dysthymic, sexually abused girls (De Bellis et al 1994a). Children and adolescents with maltreatment-related PTSD show evidence of increased catecholamine and cortisol activity. A recent study identified significantly greater concentrations of urinary dopamine and norepinephrine concentrations over 24 hours in children with maltreatment-related PTSD than non-maltreated children with overanxious disorder and control subjects, as well as greater concentrations of 24-hour urinary free cortisol in children with maltreatment-related PTSD compared to control subjects (De Bellis et al 1999a). Other investigators reported higher levels of salivary cortisol throughout the day in children with maltreatment-related PTSD or subthreshold PTSD (Carrion et al 2002) and findings of decreased platelet adrenergic receptors and increased heart rate following orthostatic challenge in physically and sexually abused children with PTSD compared with non-maltreated subjects (Perry 1994).

In the developing brain, elevated levels of catecholamines and cortisol may lead to adverse brain development through the mechanisms of accelerated loss (or metabolism) of neurons (Edwards et al 1990; Sapolsky et al 1990; Simantov et al 1996; Smythies 1997), delays in myelination (Dunlop et al 1997), abnormalities in developmentally appropriate pruning (Lauder 1988; Todd 1992), and/or the inhibition of neurogenesis (Gould et al 1997, 1998; Tanapat et al 1998). Furthermore, stress decreases brain-derived neurotrophic factor expression (Smith et al 1995). Thus, the overwhelming stress of child maltreatment experiences may have adverse influences on a child's brain maturation. Until recently, investigators have generally studied childhood brain function with psychoeducational instruments (i.e., intelligence and achievement tests). The results of these studies suggest that maltreated children demonstrate a variety of intellectual and academic impairments, including lower intelligence quotient (IQ) (Augoustinos 1987; Carrey et al 1995; Money et al 1983; Perez and Widom 1994; Pianta et al 1989; Trickett et al 1994); however, studies applying neuropsychological methods suggest that children and adolescents with PTSD show deficits in executive functioning and attention (Beers and De Bellis 2002) and everyday memory (Moradi et al 1999).

More recently, magnetic resonance imaging (MRI) has provided a safe and novel approach to measuring brain maturation in healthy and psychologically traumatized living children. To date, only two studies involving maltreated children have been reported. The results of these studies suggest that pediatric maltreatment-related PTSD is associated with adverse brain development. These include findings of smaller intracranial and cerebral volumes, and smaller total midsagittal area of corpus callosum and middle and posterior regions and larger lateral ventricular volumes than non-maltreated control subjects (De Bellis et al 1999b) and smaller brain and cerebral volumes and attenuation of frontal lobe asymmetry in children with maltreatment-related PTSD or subthreshold PTSD compared with archival control subjects (Carrion et al 2001a). In these cross-sectional studies, however, causal relationships between maltreatment, psychiatric symptoms, and brain changes cannot be ascertained. Studies in developmental traumatology are inherently complicated, because it is difficult to separate out the effects of heterogeneous sources of maltreatment from other confounding factors that are commonly present in maltreating families. These include low socioeconomic status (SES), substance abuse, low educational levels, poor parenting skills, and legal and social service entanglements. For example, these previous MRI studies did not control for socioeconomic status, which may also influence brain maturation through ecological variables. An important mission for the field of developmental traumatology research is to unravel these complex interactions. Thus in this brain maturation study, we recruited an independent and unique sample of children and adolescents with maltreatment-related PTSD for brain maturation studies who were medically healthy, psychotropic naïve, free of significant prenatal substance exposure and adolescent-onset substance abuse or dependence, and compared them to a relatively large group of sociodemographically matched, healthy, non-maltreated control subjects. It was hypothesized that maltreated children with PTSD would show decreases in volumes of structures that may be vulnerable to stress during developmental processes, such as the cerebral, frontal, and temporal cortex, amygdala and hippocampus, and corpus callosum. The basal ganglia were also measured as comparison structures. It was further hypothesized that PTSD symptoms and trauma characteristics would significantly correlate with anatomical brain measurements.

Methods and Materials

Subjects

An independent and previously unreported sample of psychotropic-naïve, maltreated children and adolescents with PTSD (n = 28) and healthy, non-maltreated control subjects (n = 66) successfully completed a volumetric MRI brain scan (Table 1). Control children were recruited by advertisement from the community. These children were without a current or lifetime episode of Axis I diagnosis as well as without a history of trauma or maltreatment. Because of the high degree of known developmental variability in volume of brain structures (Lange et al 1997), two to three control subjects were case matched for each PTSD subject for age (within 6 months) and gender. Groups were similar on measures of handedness, height, weight, Tanner Stage,

Table 1. Demographic Characteristics of Children and Adolescents with Maltreatment-Related PTSD and Non-Maltreated Sociodemographically Similar Healthy Control Subjects

	PTSD	Non-Maltreated Healthy Control Subjects	Statistic	*p*
n	28	66	—	—
Age (years)	11.47 ± 3.00	11.58 ± 2.83	$t(92) = .16$	.87
(range in years)	(4.9–16.5)	(4.3–17.0)		
Race				
White/African American/biracial	23/2/3	50/5/11	F.E.T.	ns
Weight (lbs)	99.78 ± 38.2	103.6 ± 37.9	$t(92) = .45$	.66
(range)	(33–224)	(36–195)		
Height (in)	58.35 ± 7.10	59.31 ± 7.64	$t(92) = .57$	.57
(range)	(37.8–70)	(40.6–74.5)		
Handedness (right/left)	25/3	62/4	F.E.T.	ns
SES	37.82 ± 9.69	38.95 ± 8.80	$t(92) = .55$	.58
(range)	(17–53)	(27–64)		
Sex (male/female)	14/14	31/35	$X^2 = .07$	.79
Verbal IQ	109.3 ± 16.3	115.2 ± 11.7	$t(92) = 1.99$	.05
(range)	(80–152)	(97–147)		
Performance IQ	113.2 ± 19.3	116.5 ± 16.7	$t(92) = .84$	.40
(range)	(72–155)	(79–152)		
Fullscale IQ	112.6 ± 15.8	117 ± 14	$t(1,102)=5.27$	.18
(range)	(78–137)	(90–153)		
Tanner Stage (I/II/III/IV/V)	10/5/7/4/2	24/11/18/7/6	F.E.T.	ns

PTSD, posttraumatic stress disorder; F.E.T., Fisher's Exact test; SES, socioeconomic status; IQ, intelligence quotient.

race, history of full-term pregnancy, and parental SES, as measured by the Hollingshead four-factor index (Hollingshead 1975). Verbal IQ measures of PTSD subjects were lower compared to the control group. Lower IQ may, in part, be a consequence of chronic child abuse experiences. (For further discussion see De Bellis et al 1999b).

Clinical Evaluation

Subjects and their legal guardians were evaluated by a board-certified child psychiatrist (MDDB) using a detailed trauma interview as described (De Bellis 1997) and by a trained Master's level clinician (who was blind to clinical status before the structured interview) using a modified version of the Schedule for Affective Disorders and Schizophrenia for School-Age, Present and Lifetime versions (Kaufman et al 1997a). Consensus meetings were held after the structured interview (MDDB and GM) with the clinician, and all discrepancies were resolved with information written in the medical records or on reinterviewing the child or parent to clarify information. A pregnancy history interview was completed. All subjects completed the Childhood Depression Inventory (Kovacs 1985) during the initial screening. Parents of subjects completed the Child Behavior Checklist (Achenbach and Edelbrock 1983), and the Child Dissociative Checklist (Putnam and Peterson 1994). All subjects also underwent the Vocabulary, Digit Span, Block Design, and Object Assembly subsets of the Wechsler Intelligence Scale for Children for an estimate of IQ (Wechsler 1974) and the 12 handedness items from the Revised Physical and Neurologic Examination for Subtle Signs inventory (Denckla 1985), where 8 out of 12 items were defined as right handed.

Patients with PTSD were recruited from mental health agencies that serve maltreated children in the city of Pittsburgh and its neighboring counties. Inclusion criteria included the following: 1) A DSM-IV diagnosis of chronic PTSD that resulted from child maltreatment (interpersonal violence), defined as physical abuse, sexual abuse, emotional abuse, and neglect (i.e., witnessing domestic violence is defined by child protective services as abuse by commission and emotional neglect by omission); 2) reported and indicated child maltreatment experiences by Child Protective Services, before initiation of treatment and this investigation; 3) no lifetime history of treatment with psychotropic medications; 4) the availability of at least one non-abusing caregiver who could cooperate with this protocol; and 5) living in a stable home environment, defined as not in danger from perpetrator(s) for a period of at least 3 months before this study.

All PTSD subjects had a DSM-IV diagnosis of chronic PTSD. The mean age at onset and duration of the maltreatment trauma that led to PTSD were 3.9 ± 2.5 and 4.3 ± 2.3 years, respectively. The mean length of time between maltreatment disclosure and MRI scan was 3.2 ± 2.6 years. The duration of PTSD was estimated to be 7.18 ± 2.87 years, with a range of 2.9–14.5 years. The majority of maltreated subjects experienced PTSD secondary to sexual abuse (18 of 28). Other PTSD traumas included physical abuse (2 of 28) and witnessing domestic violence (13 of 28); however, most PTSD subjects, including many of the sexually abused subjects, witnessed domestic violence (18 of 28). Some subjects (5 of 28) met DSM-IV PTSD criteria for witnessing domestic violence and sexual abuse. Information was obtained from caregiver(s) and from review of Child Protective Service or other available medical/psychiatric records.

Of the 28 PTSD subjects, 25 met criteria for three or more lifetime DSM-IV Axis I disorders (mean 3.19 ± 1.05; range 1–5). Subjects with PTSD were primarily co-morbid for mood

disorders (n = 22, 79%). These included dysthymic disorder (n = 8), major depressive disorder (n = 1), and dysthymia with major depression (n = 13). Other Axis I disorders included oppositional defiant disorder (n = 7), attention-deficit/hyperactivity disorder, predominantly inattentive type (n = 5), attention-deficit/hyperactivity disorder, combined type (n = 3), and separation anxiety disorder (n = 6). A history of suicidal ideation was noted in 18 subjects, and 4 out of the 28 had a history of suicide attempts.

Exclusion criteria were these: 1) presence of a significant medical illness, birth complications, or history of head trauma with loss of consciousness or, in females, history of adolescent pregnancy; 2) gross obesity (weight greater than 150% of ideal body weight) or growth failure (height under third percentile); 3) Wechsler Full-Scale IQ lower than 70; 4) anorexia nervosa, pervasive developmental disorder, schizophrenia, or adolescent-onset alcohol or substance abuse or dependence; 5) prenatal exposure to either alcohol and/or other substance use on a greater than two times per month basis during the first 3 months (before discovery) of pregnancy and any prenatal substance exposure during a known pregnancy with the subject; and 6) any contraindication for MRI scans (e.g., floating metallic bodies, severe claustrophobia). This protocol was approved by the University of Pittsburgh Institutional Review Board. Parent(s) or legal guardian(s) gave written informed consent. Children under age 14 years assented before participating in this protocol. Adolescents (14 years of age and older) gave written informed consent along with the written informed consent of their parent or legal guardian. Thus no subject consented to participate independently of a parent or legal guardian. Subjects received monetary compensation for participation.

MRI Acquisition

All volumetric MRI scans were performed using a GE 1.5 Tesla Unit (Signa System, General Electric Medical Systems, Milwaukee, WI) running version 5.4 software located at the University of Pittsburgh Medical Center Magnetic Resonance Research Center. The subject's head was aligned in a head holder with foam padding and the use of soft towels and chin and forehead straps to minimize head movement. The subject's nose was positioned at "12:00" for alignment, and a gradient echo localizing axial slice verified this plane. A sagittal series (using echo time [TE] = 18 msec, repetition time [TR] = 400 msec, flip angle = 90 degrees, acquisition matrix = 256 × 192, number of excitations [NEX] = 1, field of view [FOV] = 20 cm, slices = 21) verified patient position, cooperation, and image quality. We required that the midsagittal slice show full visualization of the cerebral aqueduct and the anterior and posterior commissures, in which a line was estimated requiring the anterior commissure–posterior commissure line to be within 3 degrees of 180. If these criteria were not met, the subject was realigned until these criteria were met. Coronal sections were then obtained perpendicular to the anterior commissure–posterior commissure line to provide a more reproducible guide for image orientation. A three-dimensional spoiled gradient recalled acquisition in the steady-state pulse sequence was used to obtain 124 contiguous images with slice thickness of 1.5 mm in the coronal plane (using TE = 5 msec, TR = 25 msec, flip angle = 40 degrees, acquisition matrix = 256 × 192, NEX = 1, FOV = 24 cm). Axial proton density and T2-weighted images were obtained to enable exclusion of structural abnormalities on MRI. A neuroradiologist reviewed all scans and ruled out clinically significant abnormalities. Subjects watched videos of their favorite movies during scanning. Subjects were motivated to remain still by allowing them to see their brain images after their scan. Subjects tolerated the procedure well, and all scans were obtained with minimum head movement artifact. No sedation was used. Scanning was supervised by a child psychiatrist (MDDB).

The imaging data were transferred from the MRI unit to a computer workstation (Power Macintosh, Apple Computer, Cupertino, CA) and analyzed using IMAGE software (version 1.61) developed at the National Institutes of Health (Rasband 1996) that provides valid and reliable volume measurements of specific structures using a manually operated (hand tracing) approach. All measurements were made by trained and reliable raters, who were blind to subject information. These methods were previously described by our group (De Bellis et al 1999b, 2000a, 2000b, 2001b).

Intraclass correlation of interrater and intrarater reliability for independent designation of regions on segmented images obtained from 20 subjects were 0.99 and 0.99, respectively, for intracranial volume, cerebral volume, cortical gray matter, cortical white matter, prefrontal lobe volume, prefrontal lobe gray matter, prefrontal lobe white matter, prefrontal CSF, right temporal lobe, left temporal lobe, and total temporal lobe. Intraclass correlation of interrater and intrarater reliability for independent designation of regions on segmented images obtained from 20 subjects were (respectively) 0.96 and 0.98 for right, left, and total amygdala and hippocampal volumes; 0.91 and 0.97 for right, left, and total caudate; 0.91 and 0.97 for right, left, and total putamen; 0.95 and 0.98 for lateral ventricle volumes; and 0.99 and 0.98 for total corpus callosum area, 0.97 and 0.99 for region 1 (rostrum), 0.98 and 0.99 for region 2 (genu), 0.95 and 0.99 for region 4 (anterior midbody), 0.93 and 0.97 for region 5 (posterior midbody), 0.97 and 0.99 for region 6 (isthmus), and 0.98 and 0.99 for region 7 (splenium).

Data Analysis

Demographic variables were compared using Student's t test, Pearson Chi Square, Fisher's Exact Test, or Wilcoxon/Kruskal–Wallis Rank Sums Tests, as appropriate. Number of PTSD symptoms were grouped into the DSM-IV criteria B (intrusive symptoms), C (avoidant symptoms), and D (increased arousal symptoms) clusters. Histograms were obtained to assess normality of the data and to observe any outlying observations. Formal hypothesis testing was carried out by t tests in two stages: first with the raw data, then again adjusting for total cerebral volume, to determine differences between PTSD subjects and control subjects. More involved regression analyses were used to test differences between groups, adjusting for gender and verbal IQ scores. In testing for group differences in the normal right/left structural asymmetry, right and left structural volumes were analyzed by two-way, repeated-measures analyses of covariance, with group as the between-subjects factor, side (right and left) as

the repeated factor, and appropriate brain structure as the covariate. Adjusted least-squares brain structural means that differed significantly between the groups were correlated with clinical data using Spearman correlations because of the non-normal distribution of clinical measures. All significance testing was two-tailed, with $\alpha = .05$. All data are presented as mean ± SD unless otherwise specified.

Results

Brain Measurements

Compared with non-maltreated control subjects, subjects with maltreatment-related PTSD had smaller intracranial, cerebral, and prefrontal cortex volumes, prefrontal cortical white matter and right temporal lobe volumes, and smaller areas of the corpus callosum and its subregions 2, 4, 5, 6, and 7, than non-abused control subjects. Prefrontal cortical lobe CSF was greater in subjects with maltreatment-related PTSD than in control subjects (Tables 2 and 3).

Intracranial and cerebral volumes were both 6.0% smaller in subjects with maltreatment-related PTSD compared with control subjects. When cerebral volume was taken into account, right, left, and total lateral ventricles and prefrontal cortical CSF were larger in subjects with PTSD than in control subjects. The total midsagittal area of corpus callosum and its subregions 4, 5, 6, and 7 were smaller, whereas region 2 showed a trend to be smaller, in subjects with PTSD than in control subjects (Table 3). No differences were seen in amygdala, hippocampal, caudate, or putamen volumes. The normal right > left asymmetries were seen for all structures measured except the putamen, where the expected left > right asymmetry was found. There were no significant side × group interactions.

When verbal IQ was taken into account, intracranial and cerebral volumes in subjects with maltreatment-related PTSD showed smaller differences than control subjects [$F(1,91) = 2.7$, $p = .10$; $F(1,91) = 2.6$ $p = .10$, respectively] but did not meet statistical significance. When cerebral volumes and verbal IQ were taken into account, prefrontal cortical lobe CSF was greater in PTSD subjects [$F(1,90) = 10.97$, $p = .001$], and right [$F(1,90) = 3.5$, $p < .07$], left [$F(1,90) = 3.2$, $p < .08$], and total ventricular [$F(1,90) = 3.6$, $p < .06$] volumes in subjects with maltreatment-related PTSD were suggestive of significantly larger differences than those in control subjects. When cerebral volumes and verbal IQ were taken into account, total midsagittal area of corpus callosum [$F(1,90) = 7.15$ $p < .009$] and its subregions 4, anterior midbody [$F(1,90) = 5.68$, $p < .02$], subregion 5, posterior midbody [$F(1,90) = 5.84$, $p < .02$], subregion 6, isthmus [$F(1,90) = 7.53$, $p = .007$] and subregion 7, splenium [$F(1,90) = 9.0$, $p < .004$] were smaller in subjects with maltreatment-related PTSD than in control subjects. When cerebral

Table 2. Global Morphometric Measures of Maltreated Children with PTSD and Non-Maltreated Healthy Control Subjects

Structures (cm^3)	Unadjusted means ± SD		Statistic, *p* Value	Adjusted least square means ± SD[a]		Covariate, *t* (91), *p* Value
	Control Subjects	PTSD		Control Subjects	PTSD	
Intracranial volume	1483.8 ± 174.9	1399 ± 155.2	t (92) = 2.22 $p < .03$			
Cerebral volume	1254.8 ± 156.6	1183.7 ± 131.1	t (92) = 2.11 $p < .04$			
Cortical gray matter	810 ± 104	771.4 ± 86.8	t (92) = 1.74 $p < .09$	798.5 ± 58.7	799.0 ± 50.7	Group: $t = -.02$, $p = .99$ Cerebral vol: $t = 13.74$, $p < .0001$
Cortical white matter	444.4 ± 92.2	418.8 ± 59.1	t (92) = 1.35 $p = .18$	432.6 ± 60.7	446.7 ± 45.6	Group: $t = .42$, $p = .68$ Cerebral vol: $t = 11.52$, $p < .0001$
Lateral ventricles (total)	10.31 ± 4.53	11.7 ± 6.33	t (92) = −1.21 $p = .23$	10.06 ± 4.08	12.28 ± 6.08	Group: $t = 2.09$, $p < .04$ Cerebral vol: $t = 3.84$, $p = .0002$
Right lateral ventricles	5.10 ± 2.33	5.88 ± 3.42	t (92) = −1.27 $p = .21$	5.01 ± 2.17	6.10 ± 3.32	Group: $t = 2.00$, $p < .05$ Cerebral vol: $t = 3.23$, $p < .002$
Left lateral ventricles	5.20 ± 2.42	5.82 ± 3.17	t (92) = −1.04 $p = .30$	5.05 ± 2.15	6.18 ± 3.03	Group: $t = 1.98$, $p = .05$ Cerebral vol: $t = 4.09$, $p < .0001$

[a]Means are adjusted for cerebral volume.
PTSD, post traumatic stress disorder; vol, volume.

volumes and verbal IQ were taken into account, the genu of the corpus callosum (region 2) was smaller in subjects with maltreatment-related PTSD than in control subjects [$F(1,90) = 5.25$, $p = .02$].

Relationships between Brain Structures and Demographic and Clinical Factors

Subjects with maltreatment-related PTSD showed significantly lower levels of functioning on the Global Assessment of Function scale, greater child ratings of depression on the Childhood Depression Inventory, greater parent ratings for internalizing and externalizing symptoms on the Child Behavior Checklist, and more evidence of dissociation on the Child Dissociative Checklist than control subjects (Table 4).

Intracranial ($r_s = -0.42$, $p < .03$) and cerebral volumes ($r_s = -0.42$, $p < .03$) correlated negatively with the duration of the maltreatment experience (in years) that led to PTSD diagnosis. Intracranial ($r_s = 0.39$, $p < .04$) and cerebral volumes ($r_s = 0.37$, $p = .01$) correlated positively with age of onset of maltreatment. These significant relationships persisted when means were additionally adjusted for chronological age of PTSD subjects [intracranial volumes and duration of maltreatment: $F(1,25) = 10.18$, $p < .004$; intracranial volumes and age of onset of maltreatment: $F(1,25) = 6.09$, $p < .02$; cerebral volumes and duration of maltreatment: $F(1,25) = 9.55$, $p < .005$; cerebral volumes and age of onset of maltreatment: $F(1,25) = 5.44$, $p < .03$]. Frontal lobe CSF volume correlated positively with age of onset of maltreatment ($r_s = 0.52$, $p = .005$). This significant relationship persisted when means were additionally adjusted for cerebral volumes and chronological age of PTSD subjects [$F(1,25) = 12.24$, $p < .002$].

The splenium of the corpus callosum correlated negatively with symptoms of childhood dissociation ($r_s = -0.37$, $p = .05$). The expected positive correlations between IQ subscales and cerebral volume were seen for performance ($r_s = 0.58$; $p = .0001$) and full-scale ($r_s = 0.40$; $p < .04$) but not for verbal ($r_s = 0.19$; $p = .33$) IQ in the PTSD group. No significant correlations were seen between verbal, performance, or full-scale IQ and maltreatment variables in this sample.

Male subjects had larger intracranial volumes than female subjects, as expected. Significant gender × group effect revealed findings suggestive of larger right [$F(1,89) = 3.37$, $p < .07$], left [$F(1,89) = 3.11$, $p = .08$], and total lateral [$F(1,89) = 3.64$, $p < .06$] ventricular volumes for group but larger right [$F(1,89) = 5.32$, $p = .02$], left [$F(1,89) = 6.67$, $p = .01$], and total lateral [$F(1,89) = 6.69$, $p = .01$] ventricle differences in maltreated male subjects with PTSD than maltreated female subjects with PTSD. Maltreated male subjects with PTSD demonstrated larger lateral ventricular volumes than male control subjects [$F(1,42) = 5.83$, $p = .02$]. When maltreated female subjects with PTSD were compared to control female subjects, no lateral ventricular volume differences were seen between groups [$F(1,46) = .29$, $p = .59$]. There was also a trend for a gender × group effect for smaller cerebral volumes in maltreated male subjects with PTSD than in maltreated female subjects with PTSD [group: $F(1,90) = 7.34$, $p = .008$; gender × group: $F(1,90) = 3.17$, $p < .08$]. Interestingly, significant gender × group effect revealed smaller left [$F(1,89) = 4.06$, $p < .05$] and total hippocampal volumes [$F(1,89) = 3.98$, $p < .05$] in maltreated female subjects with PTSD than maltreated male subjects with PTSD, but no effect of group for left [$F(1,89) = .08$, $p = .78$] or total [$F(1,89) = .32$, $p = .57$] hippocampal volumes; however, when maltreated female subjects with PTSD were compared to control female subjects, no hippocampal differences were seen between groups [PTSD mean: 7.43 ± 1.2 cm^3, control mean: 7.88 ± 1.3 cm^3; $F(1,46) = .68$, $p = .42$]. Unlike the findings in the previous study, where maltreated male subjects with PTSD had greater corpus callosum differences (De Bellis et al 1999b), no significant gender × group effect was seen for corpus callosum area [$F(1,89) = .71$, $p = .40$]; however, when the area of the corpus callosum was only compared in maltreated male subjects with PTSD and control male subjects, the corpus callosum was significantly smaller [$F1,42 = 5.84$, $p = .02$], whereas when the area of the corpus callosum was only compared in maltreated female subjects with PTSD and control female subjects, the corpus callosum was smaller but did not meet statistical significance [$F1,46 = 2.08$, $p = .16$]. No other significant gender × group interactions were seen.

Discussion

Medically healthy children and adolescents with the diagnosis of maltreatment-related PTSD had smaller intracranial, cerebral, and prefrontal cortex, prefrontal cortical white matter and right temporal lobe volumes, and smaller areas of the corpus callosum and its subregions 2, 4, 5, 6, and 7, and larger frontal lobe CSF volumes than sociodemographically matched, non-maltreated control subjects. After adjustment for cerebral volume, total midsagittal area of corpus callosum and middle and posterior regions remained smaller, whereas right, left, and total lateral ventricles and frontal lobe CSF volume were proportionally larger in subjects with PTSD than in control subjects. Brain volumes positively correlated with age of onset of PTSD trauma and negatively correlated with duration of abuse. The splenium (region 7) of the corpus callosum correlated negatively with symptoms of childhood disso-

Table 3. Brain Structures of Maltreated Children with PTSD and Non-Maltreated Healthy Control Subjects

Structures (cm^3)	Unadjusted Means ± SD		Statistic p Value	Adjusted least square Means ± SD[a]		Covariate, t (91), p Value
	Control Subjects	PTSD		Control Subjects	PTSD	
Prefrontal lobe volume	179.9 ± 31.0	166.2 ± 26.5	t (92) = 2.04 $p < .05$	180.5 ± 42.3	164.7 ± 38.8	Group: $t = -.59$, $p = .56$ Cerebral vol: $t = 14.11$, $p < .0001$
Prefrontal lobe gray matter	120.3 ± 20.1	114.6 ± 17.8	t (92) = 1.32 $p = .19$	120.2 ± 31.0	115.0 ± 28.7	Group: $t = -.23$, $p = .82$ Cerebral vol: $t = 9.95$, $p < .0001$
Prefrontal lobe white matter	59.5 ± 16.9	51.6 ± 11.5	t (92) = 2.27 $p < .03$	60.4 ± 27.3	49.6 ± 17.3	Group: $t = -1.15$, $p = .25$ Cerebral vol: $t = 8.99$, $p < .0001$
Prefrontal lobe CSF	4.42 ± 2.8	7.31 ± 5.6	t (92) = 2.61 $p = .01$	3.5 ± 5.5	9.4 ± 11.1	Group: $t = -3.56$, $p = .0006$ Cerebral vol: $t = 1.34$, $p = .18$
Temporal lobe (total)	184.3 ± 25.8	174.2 ± 18.8	t (92) = 1.86 $p < .07$	184.47 ± 34.3	173.77 ± 28.6	Group: $t = -.15$, $p = .88$ Cerebral vol: $t = 14.85$, $p < .0001$
Right temporal lobe	95.6 ± 14.1	89.59 ± 9.85	t (92) = 2.04 $p = .04$	95.82 ± 18.9	88.95 ± 14.7	Group: $t = -.49$, $p = .62$ Cerebral vol: $t = 14.64$, $p < .0001$
Left temporal lobe	88.8 ± 12.7	84.6 ± 10.1	t (92) = 1.54 $p = .13$	88.71 ± 18.2	84.68 ± 16.7	Group: $t = .15$, $p = .88$ Cerebral vol: $t = 11.73$, $p < .0001$
Amygdala (total)	4.47 ± 1.01	4.47 ± 1.12	t (92) = −.02 $p = .98$	4.39 ± 1.8	4.64 ± 2.1	Group: $t = 1.25$, $p = .21$ Cerebral vol: $t = 5.71$, $p < .0001$
Right amygdala	2.44 ± .58	2.39 ± .63	t (92) = .35 $p = .73$	2.41 ± .99	2.46 ± 1.2	Group: $t = 1.01$, $p = .31$ Cerebral vol: $t = 6.62$, $p < .0001$
Left amygdala	2.03 ± .52	2.09 ± .61	t (92) = −.49 $p = .62$	1.98 ± .98	2.19 ± 1.2	Group: $t = 1.29$, $p = .19$ Cerebral vol: $t = 3.64$, $p = .0005$
Hippocampus (total)	8.19 ± 1.2	7.95 ± 1.24	t (92) = .84 $p = .4$	8.16 ± 2.1	8.01 ± 2.3	Group: $t = .45$, $p = .66$ Cerebral vol: $t = 6.77$, $p < .0001$
Right hippocampus	4.13 ± .63	4.06 ± .63	t (92) = .52 $p = .60$	4.11 ± 1.1	4.11 ± 1.2	Group: $t = .68$, $p = .50$ Cerebral vol: $t = 5.95$, $p < .0001$
Left hippocampus	4.05 ± .63	3.90 ± .65	t (92) = 1.07 $p = .29$	4.04 ± 1.1	3.91 ± 1.2	Group: $t = .21$, $p = .84$ Cerebral vol: $t = 6.92$, $p < .0001$
Caudate (total)	9.33 ± 1.18	9.27 ± 1.55	t (92) = .20 $p = .84$	9.28 ± 2.2	9.39 ± 3.0	Group: $t = .69$, $p = .49$ Cerebral vol: $t = 4.23$, $p < .0001$
Right caudate	4.81 ± .65	4.75 ± .81	t (92) = .40 $p = .69$	4.79 ± 1.2	4.79 ± 1.6	Group: $t = .47$, $p = .64$ Cerebral vol: $t = 4.13$, $p < .0001$
Left caudate	4.52 ± .56	4.52 ± .78	t (92) = −.03 $p = .98$	4.49 ± 1.0	4.60 ± 1.5	Group: $t = .91$, $p = .37$ Cerebral vol: $t = 4.07$, $p = .0001$
Putamen (total)	7.32 ± 1.89	7.79 ± 1.47	t (92) = −1.18 $p = .24$	7.16 ± 3.8	8.16 ± 2.9	Group: $t = 1.34$, $p = .19$ Cerebral vol: $t = .85$, $p = .40$
Right putamen	3.93 ± .98	4.14 ± .77	t (92) = −1.05 $p = .30$	3.31 ± 2.0	3.82 ± 1.6	Group: $t = 1.18$, $p = .24$ Cerebral vol: $t = .10$, $p = .92$
Left putamen	3.39 ± 1.00	3.64 ± .80	t (92) = −1.20 $p = .23$	3.85 ± 1.9	3.34 ± 1.5	Group: $t = 1.37$, $p = .17$ Cerebral vol: $t = 1.55$, $p = .12$
Corpus Callosum (cm^2)	7.89 ± 1.21	7.06 ± 1.36	t (92) = 2.97 $p = .004$	8.11 ± 2.37	6.56 ± 2.70	Group: $t = -2.59$, $p = .01$ Cerebral vol: $t = 1.55$, $p = .13$
Region 1 rostrum	1.62 ± .38	1.51 ± .32	t (92) = 1.39 $p = .17$	1.64 ± .73	1.46 ± .64	Group: $t = -.85$, $p = .40$ Cerebral vol: $t = 2.51$, $p = .01$
Region 2 genu	.75 ± .16	.68 ± .16	t (92) = 1.96 $p = .05$	.77 ± .31	.63 ± .32	Group: $t = -1.89$, $p = .06$ Cerebral vol: $t = .07$, $p = .95$

Region 3 rostral body	.61 ± .15	.57 ± .18	t (92) = 1.08 p = .29	.62 ± .30	.55 ± .36	Group: t = −.99, p = .32 Cerebral vol: t = .27, p = .79
Region 4 anterior midbody	.89 ± .16	.78 ± .19	t (92) = 2.65 p = .009	.91 ± .33	.72 ± .37	Group: t = −2.31, p = .02 Cerebral vol: t = 1.37, p = .17
Region 5 posterior midbody	.80 ± .15	.71 ± .18	t (92) = 2.57 p = .01	.82 ± .29	.65 ± .36	Group: t = −2.42, p = .02 Cerebral vol: t = .38, p = .70
Region 6 isthmus	.70 ± .17	.59 ± .18	t (92) = 2.82 p = .006	.73 ± .34	.52 ± .36	Group: t = −2.70, p = .008 Cerebral vol: t = .17, p = .86
Region 7 splenium	2.21 ± .36	1.93 ± .38	t (92) = 3.43 p = .001	2.29 ± .72	1.75 ± .76	Group: t = −3.04, p = .003 Cerebral vol: t = 1.56, p = .12

PTSD, post traumatic stress disorder; vol, volume.
[a]Means are adjusted for cerebral volume.

ciation. The significant gender × group effect suggests greater lateral ventricular volume increases in maltreated male subjects with PTSD than in maltreated female subjects with PTSD.

Overall, the results independently replicate the majority of the brain structural findings from our earlier study of 43 maltreated children and adolescents with PTSD and 61 control subjects (De Bellis et al 1999b). In that study, the total midsagittal area of corpus callosum, particularly its middle and posterior subregions (4, 5, 6, and 7), were smaller in PTSD subjects than control subjects, whereas right, left, and total lateral ventricles and cortical and prefrontal cortical CSF volumes were proportionally larger in PTSD subjects than in control subjects. The association between decreased intracranial and cerebral volumes and duration of maltreatment from a very early age in children with PTSD also independently replicates the findings from our earlier study (De Bellis et al 1999b). The positive correlations between intracranial and cerebral volumes with age of onset of PTSD trauma and negative correlations with duration of PTSD trauma suggests that traumatic childhood experiences may adversely influence brain development. Smaller brain and cerebral volumes were also found in a small sample of 24 traumatized children, half of whom had subthreshold PTSD and half of whom had PTSD (Carrion et al 2001a). In this latter study, attenuation of frontal lobe asymmetry was also found. Right and left frontal lobe measures were not undertaken in this present study. As was seen in our earlier study (De Bellis et al 1999b), maltreated children and adolescents with PTSD did not show an attenuation of the normal anatomical right/left brain asymmetry for amygdala, hippocampal, or basal ganglion structures (De Bellis et al 1999b). Although the splenium (region 7) of the corpus callosum correlated negatively with symptoms of childhood dissociation, we were not able to replicate the significant negative correlations between PTSD cluster symptoms of intrusive thoughts, avoidance, hyperarousal, and/or dissociation with intracranial or cerebral volumes or total corpus callosum area and other corpus callosum subregions. Nor did we replicate our findings of significant negative correlations between duration of the maltreatment experience (in years) that led to PTSD with verbal, performance, and full-scale IQ. We also did not replicate the significant positive correlations between ventricular volumes with PTSD cluster symptoms of intrusive thoughts, avoidance, hyperarousal, or dissociation and/or duration of PTSD trauma.

The positive correlation between larger frontal lobe CSF volume with age of onset of the maltreatment experience (in years) that led to PTSD suggests that the frontal lobes may be particularly associated with PTSD. Although we were not able to measure the medial frontal

Table 4. Behavioral Measures of Maltreated Children with PTSD and Non-Maltreated Healthy Control Subjects

	Control Subjects Means ± SD	PTSD Means ± SD	Statistic	*p* Value
Children's Global Assessment Scale	90.68 ± 5.68	54.68 ± 8.12	$t(92) = 24.61$	<.0001
Child Depression Inventory	3.71 ± 2.75	11.68 ± 7.67	$t(92) = -7.43$	<.0001
Child Dissociative Checklist	1.21 ± 1.39	9.54 ± 5.30	$t(92) = -11.91$	<.0001
CBCL Withdrawal T Score	51.30 ± 3.22	60.93 ± 8.70	$t(92) = -7.85$	<.0001
CBCL Somatic Complaints	52.61 ± 4.12	61.11 ± 9.24	$t(92) = -6.19$	<.0001
CBCL Anxious/Depressed T Score	52.18 ± 4.21	63.61 ± 9.26	$t(92) = -8.26$	<.0001
CBCL Social Competence T Score	51.36 ± 2.90	60.64 ± 7.35	$t(92) = -8.81$	<.0001
CBCL Thought Problems T Score	51.8 ± 3.99	62.4 ± 10.1	$t(92) = -7.30$	<.0001
CBCL Attention Problems T Score	53.17 ± 4.82	64.04 ± 9.38	$t(92) = -7.42$	<.0001
CBCL Delinquent Behaviors T Score	52.45 ± 3.36	63.1 ± 10.4	$t(92) = -7.55$	<.0001
CBCL Aggressive Behaviors T Score	52.42 ± 4.19	64.9 ± 12.2	$t(92) = -7.37$	<.0001
CBCL Internal T Score	44.26 ± 9.27	62.96 ± 9.96	$t(92) = -8.75$	<.0001
CBCL External T Score	45.7 ± 10.1	62.4 ± 13.6	$t(92) = -6.58$	<.0001
CBCL Total T Score	44.5 ± 10.9	64.1 ± 11.5	$t(92) = -7.86$	<.0001

PTSD, post traumatic stress disorder; CBCL, Child Behavior Checklist.

cortex, recent findings of lower *N*-acetylaspartate/creatine ratios, which are suggestive of neuronal loss in the anterior cingulate region of the medial prefrontal cortex (De Bellis et al 2000c) and significant deficits within the domains of attention and executive function (Beers and De Bellis 2002), in pediatric subjects with maltreatment-related PTSD when compared with non-maltreated sociodemographically similar children support this idea. Exposure to stress impairs prefrontal cortical function in studies of humans and animals (for review see Arnsten 1998). The medial prefrontal cortex is involved in the extinction of conditioned fear responses and is implicated in the pathophysiology of PTSD (for review see Hamner et al 1999). Medial prefrontal cortical–limbic circuits are involved in the inhibition of fearful behaviors (for review see LeDoux 1998). Furthermore, neuroimaging studies provide evidence for prefrontal cortical dysfunction in adult PTSD. Positron emission tomography investigations comparing women who had been sexually abused as children and who had PTSD with women with similar history who did not have PTSD found a lower level of medial prefrontal blood flow during traumatic script-driven imagery (Shin et al 1999) and during memories of sexual abuse (Bremner et al 1999).

Children and adolescents with maltreatment-related PTSD had smaller total midsagittal area of corpus callosum and the middle and posterior subregions (4, 5, 6, and 7) than control subjects. This finding also replicates the findings from our earlier study (De Bellis et al 1999b). Decreased subregions of the corpus callosum were also reported in physically abused and neglected children who were not evaluated for PTSD compared to psychiatrically ill non-maltreated control subjects (Teicher et al 1997). Similarly, nursery-reared rhesus monkeys also showed decreased corpus callosum area measures, especially in the middle and posterior subregions, accompanied by decreased cortical white matter in the parietal and prefrontal cortex and impaired acquisition of complex cognitive tasks (Sanchez et al 1998). Although these monkeys were reared in social isolation, this paradigm can be conceived as a model of neglect. Yet, neglect to a social species may be perceived as stressful. For example, emotionally but not physically neglected institutionalized infants suffered from increased rates of infection and early death (Chapin 1917). These high rates of infection may be associated with a catecholamine-induced suppression of the immune system (for review see De Bellis and Putnam 1994).

As reported in the previous study (De Bellis et al 1999b), there was an indication that maltreated male subjects with PTSD may show more evidence of adverse brain development than maltreated female subjects with PTSD. A significant gender × group effect revealed greater lateral ventricular volumes and a trend for smaller cerebral volume in male subjects with maltreatment-related PTSD compared with maltreated female subjects with PTSD. Age-related gender differences have been reported in cerebral pruning and myelination during human development, in which boys showed significantly greater loss of gray matter volume and an increase in both white matter and corpus callosum area compared with girls (De Bellis et al 2001b). During healthy development, lateral ventricle volumes demonstrate a prominent gender difference in brain maturation, with robust increases in size in male subjects only (Giedd et al 1997). Cross-sectional investigations of human aging have suggested that there may be greater age-related atrophy in men compared to women (Coffey et al 1998). Male children utilize psychiatric services at higher rates and are at greater risk than female children for developmental neuropsychiatric disorders (Earls 1987). Furthermore, in a

study of a large sample of adult survivors of child abuse who were followed from childhood in a long-term prospective study of early (<11 years of age) child abuse and/or neglect, compared with sociodemographically matched control subjects, maltreated male subjects showed less resilience as adults than maltreated female subjects, who were similar to control male subjects on this measure (McGloin and Widom 2001). Our findings may suggest that boys may be more vulnerable to the effects of severe stress on brain development than girls. This vulnerability may lead to decreased adult resilience. Thus, being male may constitute a neurobiologic risk marker for stress-related vulnerability for adverse brain development during childhood.

In this study of childhood PTSD secondary to maltreatment, we did not find the predicted decrease in hippocampal volume. Thus, this is the third pediatric report that did not find the predicted hippocampal volume differences between PTSD and control children (Carrion et al 2001a; De Bellis et al 1999b). Smaller hippocampal volumes were reported in adults with PTSD secondary to child abuse (Bremner et al 1997) and female adult survivors of childhood sexual abuse (Stein et al 1997). The PTSD subjects in these adult investigations, like our maltreated child and adolescent PTSD subjects and the two other reports of pediatric PTSD, did not differ in the degree of psychiatric co-morbidity. In these studies and our own data, maltreated subjects with PTSD exhibited high degrees of co-morbidity, especially for co-morbid mood disorders; however, our pediatric PTSD subjects had neither the co-morbid histories of alcohol and substance abuse that are commonly present in studies of adult PTSD nor histories of significant prenatal substance exposure. Maltreated children are at increased risk for adolescent alcohol and substance use disorders (for review see De Bellis 2002). Self-medication of PTSD symptoms may contribute to the association between child maltreatment and adolescent alcohol and substance abuse and dependence disorders. Psychiatric co-morbidity for alcohol and substance abuse/dependence in adult PTSD subjects, especially during adolescence, may have contributed to smaller hippocampal findings in adult PTSD (De Bellis et al 2000b). Furthermore, the hippocampal volumes of pediatric subjects with maltreatment-related PTSD did not differ from control subjects in longitudinal studies (De Bellis et al 2001a). Thus the role for neurodevelopmental stunting by cortisol as a possible explanation for the differences in hippocampal findings between children and adults with PTSD is not supported; however, the negative hippocampal findings in pediatric studies are quite interesting, given that some of the subjects studied demonstrated greater 24-hour urinary free cortisol concentrations (De Bellis et al 1999a) and elevated salivary cortisol levels (Carrion et al 2002). This leads to speculation that elevated cortisol alone may not be solely responsible for hippocampal atrophy. Maltreatment stress may involve inhibition of neurogenesis (Gould et al 1997, 1998; Tanapat et al 1998) and decreases in brain-derived neurotrophic factor expression (Smith et al 1995). This may be related to elevated corticotrophin-releasing hormone or factor. These mechanisms may lead to global rather than specific neurodevelopmental differences between maltreated and non-maltreated children. Given that there are very few animal and clinical studies to date regarding stress and developing mammals, more research to address this issue is critically important.

Our findings of smaller intracranial and cerebral volumes may be associated with lower verbal IQ scores of our maltreated subjects with PTSD. Lower IQ and reading ability were reported in a large, prospective, sociodemographically matched study of early maltreatment (Perez and Widom 1994). Lower verbal but not performance IQ has also been reported in maltreated children (Carrey et al 1995). In this cross-sectional MRI study, it is unfortunately not possible to determine whether lower verbal intelligence in maltreated children was present before the PTSD or whether it was a consequence of PTSD.

In summary, the results of this study replicate and further extend earlier findings of alterations in brain maturation in pediatric subjects with maltreatment-related PTSD. Thus, the results of this study expanded the results of previously published studies by controlling for socioeconomic factors, medication history, birth history, and prenatal substance exposure, and provide further evidence to suggest that the overwhelming stress of child maltreatment experiences may have adverse influences on a child's brain maturation. Although this cross-sectional study does not imply causation, it is unlikely that the results reported here are primarily related to having a pediatric anxiety disorder. Our earlier work has demonstrated that nontraumatized pediatric patients with generalized anxiety disorder do not demonstrate smaller cerebral, frontal lobe, or corpus callosum measures as compared with control subjects (De Bellis et al 2000a). Overall, our pediatric patients with a diagnosis of maltreatment-related PTSD exhibited significant psychopathology for internalizing disorders (especially major depression and/or dysthymia and suicidal behaviors) and externalizing problems as well as low levels of Global Assessment of Function. Hence, alterations of chemical mediators of stress during development may have more global neurotoxic influences on development (for review see De Bellis 2001). Early interventions may theoretically attenuate these changes. For example, antianxiety and antidepressive medications that dampen the activity of biological stress systems, such as clonidine (Perry 1994)

or fluoxetine (De Bellis et al 1993), might contribute to the clinical improvement of these patients in combination with psychotherapy and social interventions. Furthermore, significant gender × diagnosis effects may reveal different neurodevelopmental pathways for maltreated boys versus maltreated girls with PTSD. Further studies examining gender differences and psychotherapeutic and psychopharmacological interventions are warranted.

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References

Achenbach TM, Edelbrock CS (1983): *Manual for the Child Behavior Checklist.* Burlington, VT: University of Vermont, Department of Psychiatry.

Armsworth MW, Holaday M (1993): The effects of psychological trauma on children and adolescents. *J Counseling Dev* 72:49–56.

Arnsten AFT (1998): The biology of being frazzled. *Science* 280:1711–1712.

Augoustinos M (1987): Developmental effects of child abuse: A number of recent findings. *Child Abuse Negl* 11:15–27.

Beers SR, De Bellis MD (2002): Neuropsychological function in children with maltreatment-related posttraumatic stress disorder. *Am J Psychiatry* 159:483–486.

Bremner JD, Narayan M, Staib L, Southwick SM, McGlashan T, Charney DS (1999): Neural correlates of memories 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.

Carrey NJ, Butter HJ, Persinger MA, Bialik RJ (1995): Physiological and cognitive correlates of child abuse. *J Am Acad Child Adolesc Psychiatry* 34:1067–1075.

Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, et al (2001a): Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. *Biol Psychiatry* 50:943–951.

Carrion VG, Weems CF, Ray RD, Glaser B, Hessl D, Reiss AL (2002): Diurnal salivary cortisol in pediatric posttraumatic stress disorder. *Biol Psychiatry* 51:575–582.

Carrion VG, Weems CF, Ray RD, Reiss AL (2001b): Toward an empirical definition of pediatric PTSD: The phenomenology of PTSD symptoms in youth. *J Am Acad Child Adolesc Psychiatry* 41:166–173.

Chapin HD (1917): Systematized boarding out vs. institutional care for infants and young children. *N Y Med J* CV 1009–1011.

Coffey CE, Lucke JF, Saxton JA, Ratcliff G, Billig B, Bryan RN (1998): Sex differences in brain aging: A quantitative magnetic resonance imaging study. *Arch Neurol* 55:169–179.

De Bellis MD (1997): Posttraumatic stress disorder and acute stress disorder. In: Ammerman RT, Hersen M, editors. *Handbook of Prevention and Treatment with Children and Adolescents.* New York: John Wiley & Sons, pp 455–494.

De Bellis MD (2001): Developmental traumatology: The psychobiological development of maltreated children and its implications for research, treatment, and policy. *Dev Psychopathol* 13:537–561.

De Bellis MD (2002): Developmental traumatology: A contributory mechanism for alcohol and substance use disorders. *Psychoneuroendocrinology* 27:155–170.

De Bellis MD, Baum A, Birmaher B, Keshavan M, Eccard CH, Boring AM, et al (1999a): A.E. Bennett Research Award. Developmental traumatology part I: Biological stress systems. *Biol Psychiatry* 45:1259–1270.

De Bellis MD, Casey BJ, Dahl R, Birmaher B, Williamson D, Thomas KM, et al (2000a): A pilot study of amygdala volumes in pediatric generalized anxiety disorder. *Biol Psychiatry* 48:51–57.

De Bellis MD, Chrousos GP, Dorn LD, Burke L, Helmers K, Kling MA, et al (1994a): Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. *J Clin Endocrinol Metab* 78:249–255.

De Bellis MD, Clark DB, Beers SR, Soloff P, Boring AM, Hall J, et al (2000b): Hippocampal volume in adolescent onset alcohol use disorders. *Am J Psychiatry* 157:737–744.

De Bellis MD, Gold PW, Geracioti TD, Listwak SJ, Kling MA (1993): Association of fluoxetine treatment with reductions in CSF concentrations of corticotropin-releasing hormone and arginine vasopressin in patients with major depression. *Am J Psychiatry* 150:656–657.

De Bellis MD, Hall J, Boring AM, Frustaci K, Moritz G (2001a): A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. *Biol Psychiatry* 50:305–309.

De Bellis MD, Keshavan MS, Beers SR, Hall J, Frustaci K, Masalehdan A, et al (2001b): Sex differences in brain maturation during childhood and adolescence. *Cereb Cortex* 11:552–557.

De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd J, Boring AM, et al (1999b): A.E. Bennett Research Award. Developmental traumatology part II: Brain development. *Biol Psychiatry* 45:1271–1284.

De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Dahl R, Axelson DA, et al (2002): Superior temporal gyrus volumes in pediatric generalized anxiety disorder. *Biol Psychiatry* 51:553–562.

De Bellis MD, Keshavan MS, Spencer S, Hall J (2000c): N-acetylaspartate concentration in the anterior cingulate in maltreated children and adolescents with PTSD. *Am J Psychiatry* 157:1175–1177.

De Bellis MD, Lefter L, Trickett PK, Putnam FW (1994b): Urinary catecholamine excretion in sexually abused girls. *J Am Acad Child Adolesc Psychiatry* 33:320–327.

De Bellis MD, Putnam FW (1994): The psychobiology of childhood maltreatment. *Child Adolesc Psychiatr Clin North Am* 3:663–677.

Denckla MB (1985): Revised physical and neurological examination for soft signs. *Psychopharmacol Bull* 21:773–800.

Dunlop SA, Archer MA, Quinlivan JA, Beazley LD, Newnham JP (1997): Repeated prenatal corticosteroids delay myelination in the ovine central nervous system. *J Matern Fetal Med* 6:309–313.

Earls F (1987): Sex differences in psychiatric disorders: Origins and developmental influences. *Psychiatric Dev* 1:1–23.

Edwards E, Harkins K, Wright G, Menn F (1990): Effects of bilateral adrenalectomy on the induction of learned helplessness. *Behav Neuropsychopharmacol* 3:109–114.

Famularo R, Fenton T, Augustyn M, Zuckerman B (1996): Persistence of pediatric post traumatic stress disorder after 2 years. *Child Abuse Negl* 20:1245–1248.

Famularo R, Fenton T, Kinscherff R (1993): Child maltreatment and the development of post traumatic stress disorder. *Am J Dis Child* 147:755–760.

Famularo R, Fenton T, Kinscherff R (1994): Maternal and child posttraumatic stress disorder in cases of maltreatment. *Child Abuse Negl* 18:27–36.

Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al (1998): Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. *Am J Prev Med* 14:245–258.

Giedd JN, Castellanos FX, Rajapakse JC, Vaituzis AC, Rapoport JL (1997): Sexual dimorphism of the developing human brain. *Prog Neuropsychopharmacol Biol Psychiatry* 21:1185–1201.

Gould E, Tanapat P, Cameron HA (1997): Adrenal steroids suppress granule cell death in the developing dentate gyrus through an NMDA receptor-dependent mechanism. *Brain Res Dev Brain Res* 103:91–93.

Gould E, Tanapat P, McEwen BS, Flugge G, Fuchs E (1998): Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. *Proc Natl Acad Sci USA* 95:3168–3171.

Hamner MB, Lorberbaum JP, George MS (1999): Potential role of the anterior cingulate cortex in PTSD: Review and hypothesis. *Depress Anxiety* 9:1–14.

Hart J, Gunnar M, Cicchetti D (1996): Altered neuroendocrine activity in maltreated children related to symptoms of depression. *Dev Psychopathol* 8:201–214.

Hillary BE, Schare ML (1993): Sexually and physically abused adolescents: An empirical search for PTSD. *J Clin Psychol* 49:161–165.

Hollingshead AB (1975): Four Factor Index of Social Status. New Haven, CT: Hollingshead, Department of Sociology, Yale University.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al (1997a): Schedule for Affective Disorders and Schizophrenia for School-age Children–Present and Lifetime version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 36:980–988.

Kaufman J, Birmaher B, Perel J, Dahl RE, Moreci P, Nelson B, et al (1997b): The corticotropin-releasing hormone challenge in depressed abused, depressed nonabused, and normal control children. *Biol Psychiatry* 42:669–679.

Kovacs M (1985): The Children's Depression Inventory (CDI). *Psychopharmacol Bull* 21:995–998.

Lange N, Giedd JN, Castellanos FX, Vaituzis AC, Rapoport JL (1997): Variability of human brain structure size: Ages 4–20 years. *Psychiatry Res Neuroimaging* 74:1–12.

Lauder JM (1988): Neurotransmitters as morphogens. *Prog Brain Res* 73:365–388.

LeDoux J (1998): Fear and the brain: Where have we been, and where are we going? *Biol Psychiatry* 44:1229–1238.

Mannarino AP, Cohen JA, Berman SR (1994): The relationship between preabuse factors and psychological symptomatology in sexually abused girls. *Child Abuse Negl* 18:63–71.

McGloin JM, Widom CS (2001): Resilience among abused and neglected children grown up. *Dev Psychopathol* 13:1021–1038.

McLeer SV, Dixon JF, Henry D, Ruggiero K, Escovitz K, Niedda T, et al (1998): Psychopathology in non-clinically referred sexually abused children. *J Am Acad Child Adolesc Psychiatry* 37:1326–1333.

Money J, Annecillo C, Kelly JF (1983): Abuse-dwarfism syndrome: After rescue, statural and intellectual catchup growth correlate. *J Clin Child Psychol* 12:279–283.

Moradi AR, Doost HTN, Taghavi MR, Yule W, Dalgleish T (1999): Everyday memory deficits in children and adolescents with PTSD: Performance on the Rivermead Behavioral Memory test. *J Child Psychol Psychiatry* 40:357–361.

Perez C, Widom CS (1994): Childhood victimization and long-term intellectual and academic outcomes. *Child Abuse Negl* 18:617–633.

Perry BD (1994): Neurobiological sequelae of childhood trauma: PTSD in children. In: Murburg M, editor. *Catecholamine Function in Posttraumatic Stress Disorder: Emerging Concepts.* Washington, DC: American Psychiatric Press, pp 233–255.

Pianta R, Egeland B, Erickson MF (1989): Results of the mother-child interaction research project. In: Cicchetti D, Carlson V, editors. *Child Maltreatment: Theory and Research on the Causes and Consequences of Child Abuse and Neglect.* Cambridge, MA: Cambridge University, pp 203–253.

Putnam FW, Peterson G (1994): Further validation of the child dissociative checklist. *Dissociation* 7:204–211.

Putnam FW, Trickett PK, Helmers K, Dorn L, Everett B (1991): Cortisol abnormalities in sexually abused girls. *144th Annual Meeting Program of the American Psychiatric Association.* Washington, DC: American Psychiatric Press, pp 107.

Queiroz EA, Lombardi AB, Santos Furtado CRH, Peixoto CCD, Soares TA, Fabre ZL, et al (1991): Biochemical correlate of depression in children. *Arq Neuro-Psiquiat* 49:418–425.

Rasband W (1996): *NIH IMAGE Manual.* Bethesda, MD: National Institutes of Health.

Sanchez MM, Hearn EF, Do D, Rilling JK, Herndon JG (1998): Differential rearing affects corpus callosum size and cognitive function of rhesus monkeys. *Brain Res* 812:38–49.

Sapolsky RM, Uno H, Rebert CS, Finch CE (1990): Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci* 10:2897–2902.

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

Simantov R, Blinder E, Ratovitski T, Tauber M, Gabbay M, Porat S (1996): Dopamine induced apoptosis in human neuronal cells: Inhibition by nucleic acids antisense to the dopamine transporter. *Neuroscience* 74:39–50.

Smith MA, Makino S, Kvetnansky R, Post RM (1995): Effects of stress on neurotrophic factor expression in the rat brain. *Ann N Y Acad Sci* 771:234–239.

Smythies JR (1997): Oxidative reactions and schizophrenia: A review-discussion. *Schizophr Res* 24:357–364.

Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B (1997): Hippocampal volume in women victimized by childhood sexual abuse. *Psychol Med* 27:1–9.

Tanapat P, Galea LA, Gould E (1998): Stress inhibits the proliferation of granule cell precursors in the developing dentate gyrus. *J Dev Neurosci* 16:235–239.

Teicher MH, Ito Y, Glod CA, Andersen SL, Dumont N, Ackerman E (1997): Preliminary evidence for abnormal cortical development in physically and sexually abused children using EEG coherence and MRI. In: Yehuda R, McFarlane C, editors. *Psychobiology of Posttraumatic Stress Disorder*, Vol 821. New York: Annals of the New York Academy of Sciences, pp 160–175.

Todd RD (1992): Neural development is regulated by classical neuro-transmitters: Dopamine D2 receptor stimulation enhances neurite outgrowth. *Biol Psychiatry* 31:794–807.

Trickett PK, McBride-Chang C, Putnam FW (1994): The classroom performance and behavior of sexually abused girls. *Dev Psychopathol* 6:183–194.

Wechsler D (1974): *Manual for the Wechsler Intelligence Scale for Children-Revised.* New York: The Psychological Corp.

Wolfe DA, Sas L, Wekerle C (1994): Factors associated with the development of posttraumatic stress disorder among victims of sexual abuse. *Child Abuse Negl* 18:37–50.

Wolfe J, Charney DS (1991): Use of neuropsychological assessment in posttraumatic stress disorder. *Psychol Assess* 3:573–580.