Developmental Traumatology Part II: Brain Development*

Michael D. De Bellis, Matcheri S. Keshavan, Duncan B. Clark, B.J. Casey, Jay N. Giedd, Amy M. Boring, Karin Frustaci, and Neal D. Ryan

Background: *Previous investigations suggest that maltreated children with a diagnosis of posttraumatic stress disorder (PTSD) evidence alterations of biological stress systems. Increased levels of catecholaminergic neurotransmitters and steroid hormones during traumatic experiences in childhood could conceivably adversely affect brain development.*

Methods: *In this study, 44 maltreated children and adolescents with PTSD and 61 matched controls underwent comprehensive psychiatric and neuropsychological assessments and an anatomical magnetic resonance imaging (MRI) brain scan.*

Results: *PTSD subjects had smaller intracranial and cerebral volumes than matched controls. The total midsagittal area of corpus callosum and middle and posterior regions remained smaller; while right, left, and total lateral ventricles were proportionally larger than controls, after adjustment for intracranial volume. Brain volume robustly and positively correlated with age of onset of PTSD trauma and negatively correlated with duration of abuse. Symptoms of intrusive thoughts, avoidance, hyperarousal or dissociation correlated positively with ventricular volume, and negatively with brain volume and total corpus callosum and regional measures. Significant gender by diagnosis effect revealed greater corpus callosum area reduction in maltreated males with PTSD and a trend for greater cerebral volume reduction than maltreated females with PTSD. The predicted decrease in hippocampal volume seen in adult PTSD was not seen in these subjects.*

Conclusions: *These data suggest that the overwhelming stress of maltreatment experiences in childhood is associated with adverse brain development.* Biol Psychiatry 1999;45:1271-1284 *© 1999 Society of Biological Psychiatry*

University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania (MDDB, MSK, DBC, BJC, NDR); Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania (MDDB, DBC, BJC); Developmental Traumatology Laboratory, Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania (MDDB, AMB, KF); and NIMH, Bethesda, Maryland (JNG).

Address reprint requests to Michael D. De Bellis, Director, Developmental Traumatology Laboratory, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, 3811 O'Hara Street, Pittsburgh, PA 15213.

Received June 18, 1998; revised December 15 1998; revised February 16, 1999; accepted February 19, 1999.

Key Words: Posttraumatic Stress Disorder (PTSD), child maltreatment, neurodevelopment, corpus callosum, hippocampus, intracranial volume

*See accompanying Editorial, in this issue.

Introduction

The development of the brain is regulated by genes, that interact profoundly with early experience. The body's major biological stress systems, the hypothalamic-pituitary-adrenal (HPA) axis, and the catecholamine system (the locus ceruleus [LC]-norepinephrine [NE]/sympathetic nervous system [SNS]) are needed for survival. Overwhelming stress, such as child maltreatment experiences, may lead to alterations of these stress systems and adversely influence brain development.

PTSD and Brain Development

Maltreatment of children, defined as neglect, physical abuse, sexual abuse, and emotional maltreatment (that includes verbal threats to the child and witnessing domestic violence) is a serious public health problem. It is both a cause and a risk factor for the diagnosis of posttraumatic stress disorder (PTSD) (De Bellis 1997; De Bellis and Putnam 1994). Trauma may have psychopathological (signs and symptoms of PTSD) as well as developmental consequences. Childhood is a unique period of progressive physical, behavioral, cognitive, and emotional development. Child abuse experiences may cause delays in, deficits of, or failures of multisystem developmental achievements in behavioral, cognitive and emotional regulation (for review see De Bellis 1997). Thus, PTSD in childhood can lead to failures in behavioral and emotional regulation (Pynoos et al 1995) as well as cognitive consequences resulting in the co-morbid psychopathology commonly seen in maltreated children (Cicchetti and Lynch 1995; National Research Council 1993; Shields et al 1994).

Paralleling these developmental stages are changes in brain development. The last decade has witnessed an impressive expansion of our knowledge regarding human brain development. The most dramatic increase in myelination, including the corpus callosum, that connects all major sub-

0006-3223/99/$20.00
PII S0006-3223(99)00045-1

divisions of the cerebral cortex, occurs between the ages of 6 months to 3 years and continues into the third decade of life; while grey matter and the proportion of cerebral grey matter to white matter, (that reflects reductions in synaptic density and pruning), decreases progressively after age 4 (Jernigan and Sowell 1997). Subcortical grey matter and limbic system structures (septal area, hippocampus, amygdala) actually show an increase in volume until the third decade (Jernigan and Sowell 1997). The prefrontal cortex has the most delayed ontogeny of all regions and its development also continues into the third decade (Goldman 1971; Alexander and Goldman 1978; Fuster 1980). The prefrontal cortex subserves executive cognitive functions such as planned behaviors (Fuster 1980), working memory (Goldman-Rakic 1994), motivation (Weinberger 1987), and discriminating between internally and externalizing derived models of the world (Knight et al 1995).

Results from previous investigations suggest that alterations of biological stress systems in victims of abuse may be permanent psychobiological sequelae of childhood maltreatment (De Bellis et al 1999; De Bellis et al 1994a; De Bellis et al 1994b; De Bellis and Putnam 1994; Hart et al 1996; Kaufman 1991; Kaufman et al 1997b; Perry 1994). In the adult brain, alterations of HPA axis and catecholamine activity may result in sensitization of mature structures. Results from studies in animals suggest that elevated levels of catecholamines and cortisol may lead to alterations in brain development, through 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), or abnormalities in developmentally appropriate pruning (Lauder 1988; Todd 1992). For example, elevated levels of glucocorticoids during traumatic stress may have neurotoxic effects and result in learning and concentration impairments secondary to damage to the hippocampi (Edwards et al 1990), the principal neural target tissue of glucocorticoids (Sapolsky et al 1990). Stress associated alterations of this structure were also noted in primates and humans. Hippocampal degeneration was seen in monkeys after sustained social stress (Uno et al 1989). Smaller hippocampal volumes and functional deficits in memory were found in adults with Cushing's Syndrome (Starkman et al 1992), combat veterans with PTSD (Bremner et al 1995; Gurvits et al 1996), adults with PTSD secondary to child abuse (Bremner et al 1997), and women survivors of childhood sexual abuse with and without a diagnosis of PTSD (Stein et al 1997). In this way, PTSD in maltreated children may be regarded as an environmentally induced complex developmental disorder. It is possible that many of the acute and chronic symptoms associated with maltreatment arise in conjunction with alterations of the above mentioned stress systems adversely influencing brain development.

In this cross sectional investigation, maltreated children and adolescents with PTSD and matched healthy controls underwent comprehensive clinical evaluations including cognitive assessments and an anatomical magnetic resonance imaging (MRI) brain scan for measures of various brain structures. It was hypothesized that maltreated children with PTSD will show decreases in volumes of structures that may be vulnerable to stress during developmental processes such as the amygdala and hippocampus, the frontal and temporal cortex, and select regions of the basal ganglia and corpus callosum (consisting of fibers connecting cortical association cortices). It was further hypothesized that PTSD symptoms and trauma characteristics will significantly correlate with anatomical brain measurements. We were not only interested in studying maltreated children with PTSD from past traumas, but also children who were not currently experiencing overwhelming stress, to ascertain if traumatic experiences were associated with persistent changes in brain development. Because this investigation was cross sectional, it is difficult to separate out the effects of heterogeneous sources of trauma and other confounding factors, e.g., poverty, substance abuse, low educational levels, poor parenting skills, and legal and social service entanglements (De Bellis and Putnam 1994). These factors greatly complicate research designs. Developmental traumatology, the systematic investigation of the psychobiological impact of chronic interpersonal violence on the developing child, is a relatively new area of study in child psychiatry that synthesizes knowledge from developmental psychopathology, developmental neuroscience, and stress and trauma research. In the emerging field of developmental traumatology, measures of trauma (type, age of onset, and duration of trauma) as well as other mediating factors such as social support and demographic measures are regarded as independent variables and behavioral, cognitive, emotional, and biological measures as dependent variables. Because PTSD in maltreated children is hypothesized to be associated with global deficits in behavioral, cognitive, and emotional functioning, alterations of biological stress systems, and adverse brain development, a cross sectional study showing an association between abuse and the dependent variables is the first scientific step in evaluating these issues. Although cross sectional investigations do not establish cause-effect relationships, they were undertaken to generate likely hypotheses that can be tested in a more expensive prospective longitudinal studies of child abuse.

Methods and Materials

Subjects

Maltreated children and adolescents with PTSD ($n = 44$) and healthy non-abused controls ($n = 61$) were recruited (Table 1). Some maltreated prepubertal PTSD subjects ($n = 13$) and matched

Table 1. Demographic Characteristics of Maltreated Children with PTSD and Non-Maltreated Healthy Control Subjects

	PTSD	Control	Statistic	*p*
N	44	61	—	—
Age (years)	12.2 ± 2.4	12.0 ± 2.3	$t_{103} = .28$	NS
(range in years)	(6.7 to 17)	(7 to 17)		
Race				
White/African American/biracial	31/7/6	48/7/6	$X^2 = .93$	NS
Weight (kg)	51.4 ± 19.2	49.2 ± 18.4	$t_{103} = .58$	NS
Height (cm)	153.9 ± 14.7	151.7 ± 22.7	$t_{103} = .57$	NS
Handedness (right/left)	41/3	60/1	$X_{1,103}^2 = 1.89$	NS
SES	33.1 ± 10.5	43.3 ± 11.0	$t_{103} = 5.10$	<.001**
(range)	(17–59.5)	(18–64)		
Gender (female/male)	19/25	25/36	$X^2 = .05$	NS
Verbal IQ	101.2 ± 13.9	114.2 ± 14.6	$t_{103} = 4.57$	<.001**
(range)	(70–129)	(87–145)		
Performance IQ	102.3 ± 18.0	120.6 ± 20.3	$t_{103} = 4.80$	<.001**
(range)	(64–140)	(69–152)		
Fullscale IQ	101.7 ± 14.5	119.0 ± 17.7	$t_{103} = 5.34$	<.001**
(range)	(71–127)	(78–153)		
Tanner Stage I/II/III/IV/V	9/15/9/6/5	18/20/11/8/4	$X_{1,103}^2 = 1.61$	NS
Birth weight (kg)	3.38 ± .41	3.39 ± .44	$t_{92} = .03$	NS
Birth (fullterm/premature/unknown)	43/1/0	59/1/1	$X_{1,102}^2 = .05$	NS

PTSD = posttraumatic stress disorder; SES = socioeconomic status.

controls ($n = 11$) were also recruited for studies of 24-hour baseline urinary free cortisol and catecholamine concentrations, results are reported elsewhere (De Bellis et al 1999). Because of the high degree of known variability in volume of brain structures (Giedd et al 1996a) one to two controls were case matched for each PTSD subject for age (within 6 months), gender, handedness (except for two left-handed PTSD subjects), height (within 5 cm), weight (within 4 kg), Tanner Stage, and race. 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. Thirty eight of the 44 PTSD subjects had co-morbid psychiatric disorders: major depressive disorder ($n = 20$), dysthymic disorder ($n = 29$), oppositional defiant disorder ($n = 23$), and attention-deficit hyperactivity disorder ($n = 14$). Twenty-eight of 44 met criteria for 3 or more DSM -III-R Axis I diagnoses (mean 2.9 ± 1.1). We were able to obtain birth weight and pregnancy history of biological mother for most of our subjects. The PTSD and control groups did not differ on birth weight or history of full term pregnancy. Six of the PTSD subjects had a history of taking psychotropics (stimulants, antidepressants, and clonidine); four of these 6 also had a history of experimenting with alcohol and 2 of those also with other drugs (cannabis, glue). The mothers of 10 PTSD and 5 control subjects had a history of either alcohol or cannabis use on a greater than 2 times a month basis during their pregnancy with the subject. PTSD subjects were lower on socioeconomic status (SES), as measured by the Hollingshead four factor index (Hollingshead 1975) compared to the control group. Subsequent analyses controlled for SES. All subjects underwent the clinical evaluation as described below.

Clinical Evaluation

Subjects were evaluated by the primary author (a board-certified child psychiatrist) using a detailed trauma interview as described (De Bellis 1997) and again 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 Episode (K-SADS-P) (Chambers et al 1985) and Lifetime Version (K-SADS-E) (Orvaschel and Puig-Antich 1987) interview with both child and parent(s) as informants. Questions concerning traumatic events and PTSD symptoms over the subjects lifetime were incorporated into an expanded assessment of PTSD completed as part of the K-SADS. Additional questions involved the types of interpersonal and non-interpersonal traumas and the nature and circumstances of the such traumatic experiences are described (Kaufman et al 1997a). Consensus meetings were held after the structured interview (M.D.D.) 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. All subjects completed the Childhood Depression Inventory (CDI) (Kovacs 1985) during the initial screening. Parents of subjects completed the Child Behavior Checklist (CBCL) (Achenbach and Edelbrock 1983), and the Child Dissociative Checklist (CDC) (Putnam and Peterson 1994), and the clinician completed the Children's Global Assessment Scale (GAF) (Shaffer et al 1983) and Hollingshead Four factor index of socioeconomic status (SES) (Hollingshead 1975). All subjects also underwent the vocabulary, digit span, block design and object assembly subsets of the Wechsler Intelligence Scale for Children (WISC-R) for an estimate of IQ (Wechsler 1974) and the 12 handedness items from the Revised Physical and Neurological Examination for Subtle Signs (PANESS) inventory (Denckla 1985) where 8 out of 12 items were defined as right handed.

Maltreated children with PTSD were recruited from the outpatient clinic of Western Psychiatric Institute and Clinic, the University of Pittsburgh Medical Center (UPMC) and private mental health agencies that serve maltreated children in the City of Pittsburgh. Inclusion criteria were the following:

1. A DSM-III-R and DSM-IV diagnosis of PTSD that resulted from child maltreatment (interpersonal violence) defined as physical abuse, sexual abuse, or emotional abuse (witnessing domestic violence).
2. Reported and substantiated child maltreatment experiences by Child Protective Services in the City of Pittsburgh, before initiation of treatment and this research study.
3. The availability of at least one non-abusing caregiver who could cooperate with this protocol.
4. Living in a stable home environment defined as not in danger from perpetrator(s) for at least a period of 3 months before this investigation.
5. Subjects were screened for any contraindication for MRI scans (floating metallic bodies, severe claustrophobia).

The following were the characteristics of maltreatment: all PTSD subjects experienced chronic adversity throughout their development and had a diagnosis of chronic PTSD. The majority of maltreated subjects (34 of 44) experienced PTSD secondary to sexual abuse (mean age of onset and duration, 4.5 $\pm$ 2.7 and 2.8 $\pm$ 2.1 years, respectively). Perpetrators of sexual abuse were mother (2 of 34), father or step-father (25 of 34), brother 5 years senior than victim (4 of 34) or uncle or other close family friend or relative whom served as a regular caregiver (3 of 34). Most PTSD subjects experienced multiple types of maltreatment. Of the sexually abused subjects, many experienced other interpersonal traumas including physical abuse (13 of 34; mean age of onset and duration, 2.7 $\pm$ 1.2 and 4.7 $\pm$ 3.6 years, respectively) and witnessing domestic violence (27 of 34; mean age of onset and duration, 2.0 $\pm$ 1.3 and 5.9 $\pm$ 3.0 years, respectively). Other PTSD traumas included physical abuse (4 of 44; mean age of onset and duration, 6.0 $\pm$ 3.6 and 4.5 $\pm$ 4.0 years, respectively) without histories of sexual abuse and witnessing domestic violence (6 of 44; mean age of onset and duration, 3.7 $\pm$ 2.0 and 5.0 $\pm$ 2.5 years, respectively). In the later cases, these subjects were involved with Child Protective Services for neglect. Some subjects met DSM-IV PTSD criteria for more than one type of maltreatment experience. Information was obtained from caregiver(s), review of Child Protective Service or other available medical/psychiatric records. During this study, all maltreated subjects were living in stable home environments (permanent placements) with non-abusing caregivers, 29 were living with their mother, 3 with a grandmother, 4 with a legally adoptive mother, 3 with an aunt, and 5 were living in group homes with regular contact with non-abusing family members.

Exclusion criteria were:

1. The use or presence of medication with central nervous system or HPA axis effects within the 2 weeks before MRI scan, including over the counter cold preparations that contain pseudoephedrine and related compounds.
2. Presence of a significant medical illness.
3. Gross obesity (weight greater than 150% of ideal body weight) or growth failure (height under 3rd percentile).
4. Full scale IQ lower than 70.
5. Anorexia nervosa, autism or schizophrenia by DSM-III-R criteria.
6. Positive trauma, maltreatment, or psychiatric illness history in subjects in the healthy volunteer control group.

This protocol was approved by the University of Pittsburgh Institutional Review Board. Parent(s) or guardian(s) and adolescents 14 years of age and older gave written informed consent. Children assented before participating in this protocol. Subjects received monetary compensation for participation.

MRI Acquisition

MRI was performed using a GE 1.5 Tesla Unit (Signa System, General Electric Medical Systems, Milwaukee, Wis) running version 5.4 software located at the UPMC MR Research Center. A sagittal scout series verified patient position, cooperation, and image quality. A 3-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 $\times$ 192, NEX = 1, FOV =24 cm). Coronal sections were obtained perpendicular to the anterior-commissure-posterior-commissure line to provide a more reproducible guide for image orientation. Axial proton density and T2-weighted images were obtained to enable exclusion of structural abnormalities on MRI. A neuroradiologist reviewed all scans to rule out clinically significant abnormalities. All subjects except one female PTSD subject who did not complete the scan secondary to anxiety, tolerated the procedure well. No sedation was used.

Image Analysis

The imaging data were transferred from the MRI unit to a computer workstation (PowerMacintosh, Apple Computer) and analyzed using the IMAGE software (version 1.45) developed at the NIH (Rasband 1996) that provides valid and reliable volume measurements of specific structures using a semi-automated segmentation approach. All measurements were made by trained and reliable raters who were blind to subject information. The raters were trained at the image analysis laboratory of NIH (Jay Giedd, M.D.) or at WPIC/UPMC (Matcheri S. Keshavan, M.D.). Methodological details are provided elsewhere (see Rosenberg et al 1997; Giedd et al 1996a; Giedd et al 1994; Keshavan et al 1994 for details).

Intracranial volumes were calculated by summing up areas of successive coronal slices, including gray and white matter and cerebral spinal fluid (CSF) volumes and multiplying by slice thickness. Cerebral volumes were measured after exclusion of cerebellum and brainstem in the same manner.

Total cerebral, prefrontal lobe, amygdala and hippocampi white and grey matter and CSF Volumes were calculated using a semi-automated segmentation algorithm. This computerized segmentation technique uses mathematically derived cutoffs for gray matter-white matter-CSF partitions with histograms of signal intensities (Rosenberg et al 1997).

Prefrontal cortex volumes were calculated by summing up areas of successive coronal slices, including gray and white matter and cerebral spinal fluid (CSF) volumes and multiplying by slice thickness. The anterior boundary of the prefrontal cortex was defined as the most anterior coronal section containing grey matter. The coronal slice showing the genu of the corpus callosum was used to mark the posterior limit of the prefrontal cortex (Rosenberg et al 1997).

Measures of temporal lobe, amygdala and hippocampus were manually traced in the coronal plane as previously described (Giedd et al 1996b). The temporal lobe was separated from frontal and parietal lobes by the sylvian fissure. The temporal stem was divided by a line connecting the most inferior point of the insular cisterns to the most lateral point of the hippocampal fissure. The coronal section including the posteriormost aspect of the corpus callosum was arbitrarily designed the temporal lobe posterior boundary (inclusive). The slice showing the most anterior mammillary bodies was used as the amygdala-hippocampus boundary. The structures were manually traced. White and gray matter was calculated as above so each slice did not include the CSF of the hippocampal sulcus. Then the areas were summed for each slice, and multiplied by slice thickness.

The basal ganglia, caudate (head and body and the nucleus accumbens) and putamen were manually traced in the coronal plane, summed for each slice, and multiplied by slice thickness, delineating the caudate nucleus medially by the lateral ventricle and laterally by white matter tracts from the globus pallidus and putamen as previously described (Giedd et al 1996a; Rosenberg et al 1997).

Lateral ventricles were obtained for right and left measurements using a manual tracing technique in the coronal plane. Measures were summed for each slice and multiplied by slice thickness. This technique was used rather than measurements of CSF to more reliably exclude the choroid plexus.

The corpus callosum was identified from a single midsagittal section selected as the slice showing full visualization of the cerebral aqueduct; after this, the rater manually traced the corpus callosum along its edges. The maximum length of the corpus callosum was taken as the line joining the most anterior and posterior points of the corpus callosum. Perpendiculars were drawn to divide this area into seven regions (rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus, and splenium) (Witelson 1989; Giedd et al 1994) (see Figure 1).

Intraclass correlation of interrater and intrarater reliability for independent designation of regions on segmented images obtained from 7 subjects were 0.99 and 0.99 for intracranial volume, cerebral volume, cortical gray matter, cortical white matter, and cortical CSF (K.F., A.M.B.); intrarater reliability from 7 subjects were 0.99 for prefrontal lobe volume, 0.99 for prefrontal lobe gray matter, 0.99 for prefrontal lobe white matter, 0.99 for prefrontal lobe CSF (A.M.B.); intraclass correlation of interrater and intrarater reliability from 20 subjects were 0.99 and 0.99 for right temporal lobe, left temporal lobe, and total temporal lobe (K.F., A.M.B.); intrarater reliability from 8 subjects were 0.97 for right amygdala and hippocampus, 0.99 for left amygdala and hippocampus, and 0.98 for total amygdala and hippocampus, respectively (A.M.B.); intrarater reliability from 8 subjects were 0.99 and 0.99 for hippocampus and amygdala gray and white matter, respectively (A.M.B.); intrarater reliability from 10 subjects were 0.99 for right caudate, 0.96 for left caudate, and 0.98 for total caudate respectively (K.F.); intrarater reliability from 10 subjects were 0.98 for right putamen, 0.99 for left putamen, and 0.99 total putamen respectively (K.F.); intrarater reliability from 20 subjects were 0.99 for right lateral ventricles, left lateral ventricles, and total lateral ventricles respectively (A.K.); intrarater reliability from 5 subjects were 0.99 for total corpus callosum area, 0.97 for region 1 (rostrum), 0.98 for region 2 (genu), 0.98 for region 3 (rostral body), 0.99 for region 4 (anterior midbody), 0.99 for region 5 (posterior midbody), 0.98 for region 6 (isthmus), and 0.99 for region 7 (splenium) respectively (A.M.B.). With the exception of intracranial volume, cerebral volume, cortical gray matter, cortical white matter, cortical CSF, right temporal lobe, left temporal lobe, and total temporal lobe, all structures were measured by one rater as described.

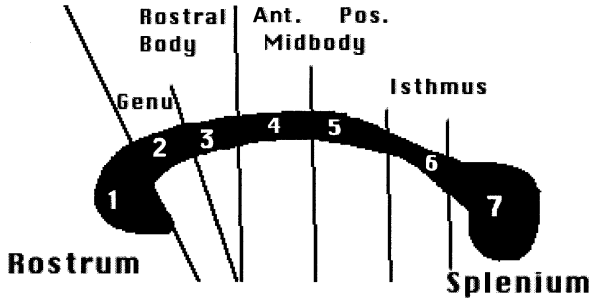

Fig. 1. Midsagittal divisions of corpus callosum for quantitative MRI measurements. Region 1 (rostrum) reflects the orbital prefrontal and inferior premotor; Region 2 (genu), the prefrontal; Region 3 (rostral body), the premotor, supplementary motor; Region 4 (anterior midbody), the motor; Region 5 (posterior midbody), the somatesthetic, posterior parietal; Region 5 (isthmus), the superior temporal, posterior parietal; and Region 6 (splenium), the occipital, inferior temporal cortical regions. Adopted from Witelson 1989 and Giedd et al 1994.

Statistical Methods

Data distributions were examined for normality. Where significantly non-normal distributions were found the data were log transformed to normalize the distributions before applying parametric tests. Demographic variables were compared using analysis of variance (ANOVA), student's *t* test or Pearson Chi Square as appropriate. PTSD symptoms were grouped into the DSM-IV criteria B (intrusive symptoms), C (avoidant symptoms), and D (increased arousal symptoms) clusters. Because the PTSD cohort had significantly smaller intracranial volumes and differed in SES, ANCOVA controlling for intracranial volume and SES were used for adjusted least squares means and these values were used in one-way or two way (group-by-side) repeated-measures analyses. In testing for covariate effect such as: age, gender, SES, and interaction (age by gender, age by diagnosis, gender by diagnosis) multivariate regression analysis was used. Adjusted least squares brain structural means differing significantly between the groups were correlated with clinical data using Spearman correlations. Spearman correlations were used because of the non-normal distribution of trauma measures. All significance testing was two-tailed with alpha = 0.05 ($p = .1$ constituted a trend). All data are presented as mean ± standard deviation (SD) unless otherwise specified. Bonferroni corrections were applied to correct for multiple correlations.

Results

Brain Measurements

Compared with controls, maltreated children and adolescents had smaller intracranial volumes than non-abused controls.

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

	Unadjusted Means (±SD)		Adjusted Least Square Means (±SD)[a]			
Structures	PTSD	Control	PTSD	Control	Statistic	*p*
Intracranial volume (cm^3)	1407.70 (162.50)	1518.13 (152.60)	1438.71 (157.45)	1496.26 (148.58)	$t_{1,101} = 2.11$	<.05
Cerebral volume	1192.15 (132.64)	1289.35 (139.81)	1270.21 (136.17)	1219.30 (128.42)	$t_{1,101} = 2.14$	<.04
Cortical gray matter	766.33 (79.34)	812.76 (96.27)	795.93 (42.57)	791.89 (50.78)	$t_{1,100} = -0.48$	NS
Cortical white matter	425.86 (76.74)	476.59 (73.81)	452.67 (41.01)	457.69 (48.01)	$t_{1,100} = -0.63$	NS
Cortical CSF	32.09 (13.95)	32.50 (10.19)	34.51 (12.07)	30.80 (9.07)	$t_{1,100} = -1.72$	<.09
Lateral ventricles (total)	12.40 (6.23)	11.23 (4.44)	13.15 (5.73)	10.74 (4.20)	$t_{1,100} = -2.34$	<.03
Right Lateral Ventricles	6.19 (3.56)	5.58 (2.15)	6.57 (3.25)	5.31 (2.04)	$t_{1,100} = -2.06$	<.05
Left Lateral Ventricles	6.21 (3.01)	5.68 (2.70)	6.58 (2.84)	5.43 (2.59)	$t_{1,100} = -2.44$	<.02

[a]Intracranial and cerebral volume means are adjusted for SES, all other means are adjusted for SES and intracranial volume.

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

	Unadjusted Means (±SD)		Adjusted Least Square Means (±SD)[a]			
Structures	PTSD	Control	PTSD	Control	Statistic	*p*
Prefrontal lobe volume	179.66 (26.83)	197.04 (30.99)	190.61 (19.17)	189.31 (16.61)	$t_{1,100} = -0.39$	NS
Prefrontal lobe gray matter	117.85 (17.29)	129.93 (24.11)	117.40 (29.80)	130.25 (39.70)	$t_{1,100} = 0.26$	NS
Prefrontal lobe white matter	49.34 (11.54)	56.20 (14.52)	53.25 (7.13)	53.44 (11.70)	$t_{1,100} = 0.12$	NS
Prefrontal lobe CSF	12.47 (6.33)	10.91 (3.38)	12.87 (6.16)	10.62 (3.30)	$t_{1,100} = -2.15$	<.05
Temporal lobe (total)	180.71 (21.22)	194.75 (20.33)	187.78 (17.79)	189.77 (12.09)	$t_{1,100} = 0.76$	NS
Right temporal lobe	93.59 (10.66)	99.60 (10.43)	96.74 (8.79)	97.38 (7.30)	$t_{1,100} = 0.46$	NS
Left temporal lobe	87.07 (11.73)	95.15 (11.05)	91.01 (10.25)	92.37 (6.55)	$t_{1,100} = 0.93$	NS
Amygdala (total)	4.26 (1.18)	4.74 (.99)	4.47 (1.11)	4.59 (.88)	$t_{1,100} = 0.67$	NS
Right amygdala	2.33 (.59)	2.56 (.57)	2.49 (.53)	2.42 (.55)	$t_{1,100} = -0.78$	NS
Right amygdala gray matter	2.18 (.55)	2.41 (.53)	2.26 (.51)	2.36 (.50)	$t_{1,100} = 1.11$	NS
Right amygdala white matter	.14 (.11)	.16 (.11)	.15 (.10)	.15 (.11)	$t_{1,100} = .1$	NS
Left amygdala	1.93 (.65)	2.19 (.55)	2.11 (.61)	2.06 (.58)	$t_{1,100} = -0.51$	NS
Left amygdala gray matter	1.87 (.63)	2.12 (.54)	1.99 (.62)	2.04 (.47)	$t_{1,100} = .28$	NS
Left amygdala white matter	.06 (.05)	.06 (.05)	.06 (.05)	.06 (.05)	$t_{1,100} = 0.14$	NS
Hippocampus (total)	8.20 (1.13)	8.39 (1.11)	8.43 (1.02)	8.21 (.98)	$t_{1,100} = -1.26$	NS
Right hippocampus (total)	4.13 (.59)	4.26 (.64)	4.28 (.54)	4.17 (.56)	$t_{1,100} = -1.13$	NS
Right hippocampus gray matter	3.77 (.53)	3.87 (.57)	3.87 (.51)	3.80 (.52)	$t_{1,100} = -.75$	NS
Right hippocampus white matter	.36 (.20)	.39 (.21)	.39 (.18)	.36 (.20)	$t_{1,100} = -1.06$	NS
Left hippocampus (total)	4.07 (.60)	4.12 (.52)	4.16 (.55)	4.05 (.48)	$t_{1,100} = -1.20$	NS
Left hippocampus gray matter	3.85 (.56)	3.83 (.63)	3.94 (.53)	3.76 (.57)	$t_{1,100} = -1.82$	= .07
Left hippocampus white matter	.21 (.12)	.23 (.13)	.23 (.11)	.22 (.13)	$t_{1,100} = -0.68$	NS
Caudate (total)	8.91 (1.13)	9.21 (1.00)	9.11 (1.02)	9.06 (.91)	$t_{1,100} = -0.28$	NS
Right caudate	4.61 (.60)	4.74 (.53)	4.71 (.54)	4.67 (.49)	$t_{1,100} = -0.44$	NS
Left caudate	4.30 (.55)	4.47 (.51)	4.40 (.50)	4.39 (.46)	$t_{1,100} = -0.10$	NS
Putamen (total)	7.60 (2.06)	7.14 (1.85)	7.57 (2.02)	7.16 (1.84)	$t_{1,100} = -1.20$	NS
Right putamen	3.50 (1.13)	3.25 (.95)	3.44 (1.11)	3.29 (.96)	$t_{1,100} = -0.83$	NS
Left putamen	4.10 (1.00)	3.89 (.96)	4.12 (.97)	3.87 (.94)	$t_{1,100} = -1.49$	NS
Corpus Callosum (cm^2)	7.14 (1.23)	7.92 (1.34)	7.29 (1.26)	7.81 (1.27)	$t_{1,100} = 2.35$	= .02
Region 1 rostrum	1.48 (.36)	1.57 (.45)	1.52 (.37)	1.54 (.41)	$t_{1,100} = .35$	NS
Region 2 genu	.68 (.16)	.73 (.17)	.68 (.16)	.73 (.16)	$t_{1,100} = 1.67$	= .1
Region 3 rostral body	.57 (.15)	.63 (.14)	.58 (.15)	.62 (.14)	$t_{1,100} = 1.35$	NS
Region 4 anterior midbody	.80 (.15)	.89 (.17)	.81 (.15)	.90 (.16)	$t_{1,100} = 3.07$	<.003
Region 5 posterior midbody	.71 (.16)	.81 (.15)	.72 (.17)	.80 (.15)	$t_{1,100} = 2.82$	<.01
Region 6 isthmus	.63 (.15)	.71 (.16)	.64 (.16)	.70 (.15)	$t_{1,100} = 2.07$	<.05
Region 7 splenium	2.00 (.40)	2.27 (.36)	2.05 (.39)	2.23 (.36)	$t_{1,100} = 2.78$	<.01

[a]Means adjusted for SES and intracranial volume.

When we compared the raw data as well as when we used age, height, weight, and gender as simultaneous covariates, cerebral and prefrontal cortex volumes, cerebral and prefrontal cortical gray matter and cortical white matter, right and left amygdala and their respective gray matter, left and right temporal lobes, and the corpus callosum and its regions 4,5, 6, and 7, were significantly smaller in maltreated children with PTSD (Table 2). Because our subjects were matched on age, gender, weight, height, Tanner Stage, handedness and

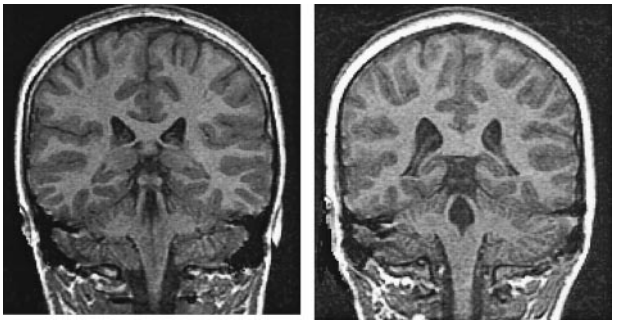

Fig. 2. Lateral ventricles measures in an 11-year-old maltreated male with chronic PTSD (right), compared with a healthy, non-maltreated matched control subject.

race, we choose to co-vary the independent variable in which the subjects differed, namely SES, and intracranial volume.

Intracranial and cerebral volumes were 7.0% and 8.0% smaller in the maltreated subjects with PTSD compared with controls. When SES was used as a covariate, intracranial and cerebral volume remained significantly smaller (Table 2). When intracranial volume and SES were taken into account, right, left, and total lateral ventricles, and cortical and prefrontal cortical CSF were larger than controls and the total midsagittal area of corpus callosum and its regions 4, 5, 6 and 7 were smaller although region 2 showed a trend to be smaller than controls (Table 3) (Figure 2). Rather than finding the predicted decrease in hippocampal volume, there was a trend toward an increase (or rather proportionally less decrease) in left hippocampal gray matter compared with controls (Table 3). 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 by diagnosis interactions. There were no

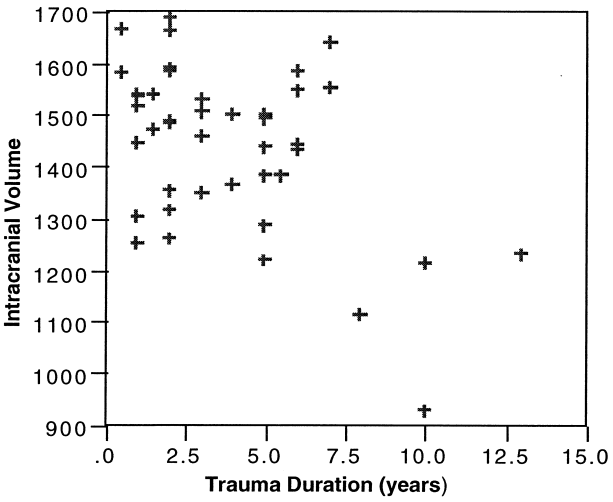

Fig. 3. The relationship between the duration of the maltreatment experiences that resulted in clinical PTSD (in years) and least squares intracranial volume means (Spearman $r = -.32$, df = 41, $p < .04$) in PTSD subjects.

differences in intracranial volumes, lateral ventricles, the corpus callosum and its regions 4, 5, 6 and 7, or the hippocampus between PTSD subjects with and without co-morbid mood disorder, with and without co-morbid ADHD, with and without co-morbid oppositional defiant disorder, with and without histories of psychotropic medication, with and without alcohol or polysubstance use, and with and without prenatal alcohol or cannabis use.

Relationships Between Brain Structures and Demographic and Clinical Factors

Maltreated subjects with PTSD showed significantly lower levels of functioning on the GAF, more suicidal

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

	PTSD (Means (±SD))	Controls (Means (±SD))	Statistic	*p*
Children's Global Assessment Scale	53.9 ± 7.2	87.3 ± 8.6	t = 21.0	<.0001
History of suicidal ideation (yes/no)	38/6	2/59	$X^2 = 74.8$	<.0001
History of suicide attempts (yes/no)	17/27	0/61	$X^2 = 28.1$	<.0001
Child depression inventory	10.4 ± 8.8	4.4 ± 4.6	t = 4.5	<.0001
Child dissociative checklist	9.3 ± 6.3	.9 ± 1.4	t = 10.2	<.0001
CBCL-withdrawal T score	61.8 ± 11.5	51.3 ± 3.2	t = 6.8	<.0001
CBCL-somatic complaints	59.3 ± 9.0	52.2 ± 3.7	t = 5.6	<.0001
CBCL-anxious/depressed T score	63.3 ± 12.1	52.0 ± 4.2	t = 5.7	<.0001
CBCL-social competence T score	61.9 ± 10.3	51.7 ± 3.5	t = 7.2	<.0001
CBCL-thought problems T score	62.0 ± 12.5	51.8 ± 4.1	t = 6.0	<.0001
CBCL-attention problems T score	65.5 ± 11.4	51.7 ± 3.8	t = 8.8	<.0001
CBCL-delinquent behaviors T score	66.7 ± 11.0	51.8 ± 3.6	t = 9.9	<.0001
CBCL-aggressive behaviors T score	66.4 ± 13.7	51.7 ± 3.7	t = 8.0	<.0001
CBCL-internal T score	61.6 ± 12.4	43.9 ± 9.2	t = 8.4	<.0001
CBCL-external T score	65.5 ± 12.9	44.1 ± 9.6	t = 9.8	<.0001
CBCL-total T score	65.3 ± 12.4	43.4 ± 9.4	t = 10.3	<.0001

CBCL = Child Behavior Checklist.

Table 5. Significant Spearman Correlation's of Adjusted Least Square Means Brain Structures of Maltreated Children with PTSD and Clinical Measures

	Intracranal Volume	Lateral Ventricles (total)	Corpus Callosum (Total)	Corpus Callosum (Region 4)	Corpus Callosum (Region 5)	Corpus Callosum (Region 6)	Corpus Callosum (Region 7)
Duration of abuse	−.32	.21	−.19	−.20	−.23	NS	−.22
Abuse age of onset	.40[a]	NS	NS	NS	NS	NS	NS
PTSD intrusive symptoms	−.20	.21	NS	NS	NS	NS	−.20
PTSD avoidant symptoms	NS	.19	NS	−.22	NS	NS	−.23
PTSD hyperarousal symptoms	NS	.21	NS	−.22	−.20	NS	−.23
Child dissociative checklist	NS	NS	−.25	−.23	NS	−.21	−.23

All values are significant at the $p < .05$ level without Boneferroni correction.
[a]For Boneferroni correction at $p < .05$ (individual test, $p < .01$ without Boneferroni correction).

ideation and behaviors, greater child ratings of depression on the Child Depression Inventory, greater parent ratings for internalizing and externalizing symptoms on the Child Behavioral Checklist (CBCL) and of dissociation on the Child Dissociative Checklist, than controls (Table 4). Intracranial volume and corpus callosum total area and regions 4, 5, and 7, correlated negatively with the duration of the maltreatment experience (in years) that led to a PTSD diagnosis (see Figure 3) (Table 5). Intracranial volume (after Bonferroni correction) correlated positively with age of onset of maltreatment (see Figure 4). This positive correlation persisted when means were additionally corrected for chronological age of PTSD subjects ($r = .37$, $p < .02$; $t_{1,39} = 2.1$, $p < .05$). Intracranial volume and region 7 of the corpus callosum correlated negatively with PTSD intrusive symptoms. Total corpus callosum and specific regions correlated negatively with PTSD symptoms, and symptoms of childhood dissociation. Volume of lateral ventricles correlated positively with duration of maltreatment and PTSD symptoms of intrusion, avoidance, and hyperviligance (Table 5). The known positive correlations between IQ subscales and intracranial volume were seen for verbal ($r = .24$; $p = .01$), performance ($r = .25$; $p < .01$), and full scale ($r = .29$; $p < .003$) IQ. Verbal ($r = -.36$; $p < .0001$), performance ($r = -.42$; $p < .0001$), and full scale ($r = -.43$; $p < .0001$) IQ also showed robust negative correlations after Bonferroni correction with duration of the maltreatment experience (in years) that led to PTSD. When Full Scale IQ (instead of SES for reasons of collinearity) was taken into account, intracranial and cerebral volumes in maltreated subjects with PTSD showed trends to be smaller than controls ($F[1,101] = 2.9$, $p < .09$; $F[1,101] = 3.0$, $p < .08$). Furthermore, when intracranial volume and Full Scale IQ were taken into account, right, left, and total lateral ventricles, and cortical and prefrontal cortical CSF were larger than controls and the total midsagittal area of corpus callosum and its regions 4, 5, 6 and 7 were still smaller ($p < .05$) although region 2 continued to show a trend ($p = .1$) to be smaller than controls.

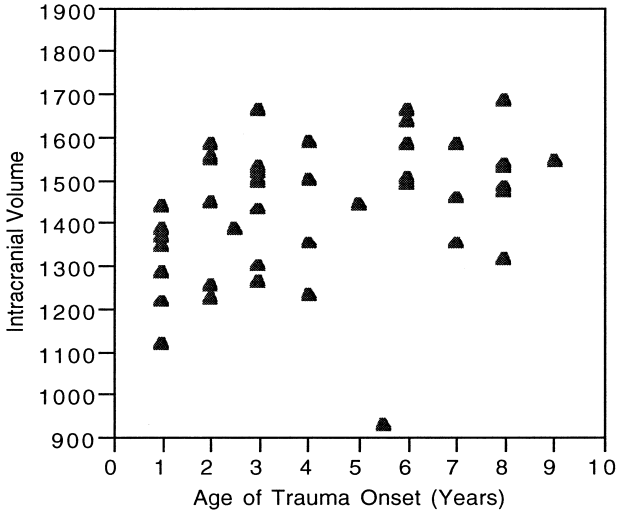

Fig. 4. The relationship between the age of onset (in years) of the maltreatment experience that resulted in clinical PTSD and least square adjusted intracranial volume means (Spearman $r = .40$, df = 41, $p < .008$) in PTSD subjects.

Males had larger intracranial volumes than females as expected. Significant sex by diagnosis effect revealed greater total corpus callosum area reduction in maltreated males with PTSD ($F[1,98] = 4.04$, df = 1,98; $p < .05$) and trends for gender by diagnosis interactions for greater cerebral volume reduction ($F[1,99] = 2.9$, $p < .09$), and corpus callosum region 6 (isthmus) area reduction ($F[1,98] = 3.7$, $p < .06$), and larger total lateral ventricles ($F[1,98] = 3.2$, $p < .08$), and non-significantly greater intracranial volume reduction ($F[1,99] = 1.8$, $p = .19$) than maltreated females with PTSD.

Discussion

Maltreated but medically healthy children and adolescents with the diagnosis of PTSD had significantly smaller intracranial and cerebral volumes than controls matched

on age, gender, handedness, Tanner Stage, race, height, and weight. PTSD subjects were found to have proportionally smaller intracranial and cerebral volumes when the means were adjusted for SES. When intracranial volume and SES were simultaneously co-varied, the total midsagittal area of corpus callosum particularly its middle and posterior regions (4, 5, 6 and 7) remained smaller than controls; although right, left, and total lateral ventricles and cortical and prefrontal cortical CSF volumes were proportionally larger than controls. Intracranial volume robustly and positively correlated with age of onset of PTSD trauma after Bonferroni correction; and negatively correlated with duration of the maltreatment experience(s) that resulted in PTSD. Furthermore, the volumes of the left and total lateral ventricles correlated positively; and total corpus callosum and its middle and posterior regions negatively, with duration of abuse. PTSD cluster symptoms of intrusive thoughts, avoidance, hyperarousal, or dissociation correlated positively with ventricular volume, and negatively with intracranial volume and total corpus callosum area and various measures of its regions. Maltreated children did not show a reversal of the normal anatomical right left brain asymmetry as suggested by studies of EEG coherence (Teicher et al 1997).

As expected, males had larger intracranial volumes than females. There was some indication that maltreated males with PTSD may show more evidence of adverse brain development than maltreated females with PTSD. A significant sex by diagnosis effect revealed greater total corpus callosum area reduction and trends for smaller cerebral volume and corpus callosum region 6 (isthmus) in maltreated males with PTSD compared with maltreated females with PTSD. In accord with these findings, we also noted a trend for a significant sex by diagnosis interaction for greater lateral ventricular volumes in traumatized male children with PTSD. Thus, our findings may suggest that males are more vulnerable to the effects of severe stress on brain development than females.

Overall, maltreated children and adolescents with a diagnosis of PTSD exhibited significantly greater psychopathology and lower levels of Global Assessment of Function scores than controls. PTSD in childhood as it is in adults is associated with many psychosocial and cognitive consequences as well as much co-morbid psychopathology (De Bellis 1997). Our maltreated sample with PTSD is similar to most studies of maltreated children that find significantly increased rates of internalizing disorders (especially major depression or dysthymia and suicidal behaviors) and externalizing disorders (oppositional behaviors) in abused children (National Research Council 1993; Shields et al 1994). Therefore, a developmental model of PTSD (Pynoos et al 1995) is fitting to comprehensively understand the neurobiological consequences of trauma.

The association between decreased intracranial volume and duration of maltreatment from a very early age in children with PTSD is intriguing. The robust positive correlation with age of onset of PTSD trauma and negative correlation with duration of abuse, suggests that traumatic childhood experiences may adversely influence brain development. Nevertheless, this is a cross sectional study, so causation cannot be proved. Intracranial volume increases steadily until age 10, with 75% of adult brain weight occurring by age 2 (Carmichael 1990) and near completion of adult intracranial volume by age 5 (Pfefferbaum et al 1994). Human brain development takes place by an overproduction of neurons in utero and then selective elimination of many of these neurons (apoptosis) by age 4 (Jernigan and Sowell 1997). Early childhood is characterized by increases in synaptic neuropil, but the process of synaptic elimination begins in late childhood and continues throughout the first 3 decades of life (Rabinowicz 1986). Neurons generally enlarge with age (Blinkov and Glezer 1968). Axons become thicker and the number of synaptic boutons increase throughout life and are presumably involved in the mechanism of learning (Werry 1991). During ages 5 to 18 years, myelination by oligodendrocytes is most influential in determining brain size. Thus, neurons, glial cells, and packing density are determinants of brain size (see Giedd et al 1996a for review). These factors are affected by many factors including genetics, hormones, growth factors, nutrients and enriched environment as well as adversely by trauma, stress, or degree of impoverished environment (Jacobson 1991; Diamond et al 1964). Our findings of lateral ventricular enlargement that also correlated positively with duration of abuse, and of increased cortical and prefrontal cortical CSF, may be indicative of a general measure of neuron or neuropil loss associated with severe stress in PTSD subjects. We recently reported that prepubertal maltreated children with PTSD (13 of whom where subjects in this study) excreted significantly greater amounts of 24-hour baseline urinary free cortisol and catecholamine concentrations than non-abused controls (De Bellis et al 1999). Furthermore, measures of urinary free cortisol and catecholamine concentrations correlated significantly with duration of maltreatment experiences (De Bellis et al 1999). In the developing brain, increased activity of steroid hormones and catecholaminergic neurotransmitters are known to modulate the developmental processes of neuronal migration, differentiation, and synaptic proliferation and may affect overall brain development adversely (Lauder 1988; Edwards et al 1990; Sapolsky et al 1990; Simantov et al 1996; Smythies 1997; Todd 1992). Smaller intracranial and cerebral volumes may also be the result of living in a chronically stressful and impoverished environment that is lacking in mental stimulation; or may be associated with chronic mental illness. Lateral ventricular enlargement has been reported in many psychiatric disorders including child-

hood-onset schizophrenia (Frazier et al 1996), and adult-onset schizophrenia (Weinberger and Wyatt 1982), Alzheimer's disease (Jernigan 1986), alcoholism (Ron 1983), bipolar disorder (Pearlson et al 1984), and major depression with psychosis (Scott et al 1983) in adults. Prenatal and postnatal malnutrition is strongly associated with retarded fetal and infant brain growth especially from loss of neurons, glial cells, and increased ventricles (Rosso 1990). Malnutrition probably does not explain the results of our findings because maltreated subjects with PTSD did not differ in birth weight, history of full term pregnancies, or birth trauma; nor did they differ in current height or weight from controls.

Our findings of smaller intracranial volume may be confounded by the lower IQ scores of our maltreated subjects with PTSD as there is an established relationship in healthy adults between IQ and brain size (Andreasen et al 1993). IQ is considered a dependent variable and may be an integral manifestation and consequence of chronic child maltreatment experiences. Failures to develop cognitive skills may lead to the significant global and cumulative cognitive, language and intellectual impairments that are consistently reported in abused and neglected children (Augoustinos 1987; Azar et al 1988; Kolko 1992) and may result in poor school performance (National Research Council 1993; Trickett et al 1994). Furthermore, Perez and Widom (1994) reported lower IQ and reading ability in a large sample of adult survivors of child abuse who were followed from childhood in a long term prospective study of early (<age 11 years) child abuse or neglect, compared with controls who were matched for age, gender, race, and SES. Most studies report temporal stability of intelligence scores in various pediatric populations including handicapped children (Atkinson et al 1990; Elliot and Boeve 1987). On the other hand, some investigations report changes in IQ in high risk samples that are related to the quantity of parent-child interaction and home environment and to the degree of maternal depression (Money et al 1983; Pianta et al 1989). In one case control study (Money et al 1983), low and persistent impairment of IQ was associated with abuse disclosure; although IQ elevations were significantly correlated with duration of "rescue" (in years) from an abusive upbringing after longitudinal follow-up. The greatest magnitude of change, from IQ 36 to 120, was seen in a girl between the ages of 3.7 and 14 years (Money et al 1983). Another study also found a negative correlation between verbal IQ score and severity of abuse (Carrey et al 1995). Thus, lower IQ may, in part, be a consequence of chronic child abuse experiences. In our study, measures of IQ positively and significantly correlated with intracranial volume. In our PTSD subjects, verbal, performance, and full scale IQ also showed robust negative correlations after Bonferroni correction with duration of the maltreatment experience (in years) that led to PTSD. When full scale IQ was taken into account, intracranial and cerebral volumes in maltreated subjects with PTSD showed trends to be smaller than controls. Also when intracranial volume and full scale IQ were taken into account, right, left, and total lateral ventricles, and cortical and prefrontal cortical CSF were larger than controls; and the total midsagittal area of corpus callosum and its regions 4, 5, 6 and 7 were still smaller although region 2 continued to show a trend to be smaller than controls. Adult studies have long reported cognitive changes in patients with PTSD (Wolfe and Charney 1991). Lower cognitive ability, particularly concentration, learning, and memory problems, has been described in several military veteran populations (Boulanger 1985; Sutker et al 1990; Sutker et al 1991), refugee groups (Goldfeld et al 1988) and in combat-related PTSD (Bremner et al 1993a; McNally and Shin 1995; Pitman et al 1991). One study suggested that premorbid lower IQ may increase the risk for combat-related PTSD (Macklin et al 1998); but these subjects were not screened for child abuse. Another study showed that child maltreatment is a risk factor for later onset PTSD in combat veterans (Bremner et al 1993b). In this cross-sectional MRI study, it is unfortunately not possible to determine whether lower intelligence in maltreated children was present before the PTSD or whether it was a consequence of PTSD. Gender has an effect on brain size independent of IQ. In our study, the female control children and adolescents had 12% smaller intracranial volumes than male controls with similar IQ scores. Based on this review and our preliminary findings, we must consider that the smaller cerebral volumes seen in these maltreated subjects with PTSD may be associated with permanent neuronal loss leading to lower IQ. Although a genetic contribution to IQ is well known, our findings support a multifactorial causation model of intelligence.

Children and adolescents with PTSD had smaller total midsagittal area of corpus callosum and the middle and posterior regions (4,5,6 and 7) than controls. The corpus callosum is easily visualized on midsagittal MRI scans; approximately 200 million fibers coursing through it remain roughly topographically consistent while connecting homologous areas of the cortex (Innocenti et al 1974). Thus abnormalities in a given area of the corpus callosum may reflect abnormalities in the specific corresponding region of the brain from where these fibers originate (de Lacoste et al 1985). The function of the corpus callosum, the major interconnection between the two hemispheres, is broadly conceptualized as facilitating the cortical communication (Ramaekers and Njiokiktjien 1991). From a neuropsychological standpoint, individuals who have experienced a commissurotomy exhibit marked behavioral discontinuities between perception, comprehension, and response (Lezak 1995). Symptoms of PTSD, dissociation, and executive difficulties that accompany PTSD might be explained in terms of such changes. We found negative correlations between posterior region 7 (splenium) and each of the PTSD clusters of

symptoms. Because axonal fibers from the occipital areas (primary and secondary visual areas) and the limbic system course through region 7, fewer neurons may be associated with less response inhibition. Thus, when a PTSD subject is presented with a traumatic reminder, less response inhibition may lead to the core PTSD symptoms of flashbacks, intrusive thoughts, and associated symptoms of avoidance, numbing, and hyperarousal. A recent PET study showing activation of limbic, paralimbic, and visual areas during trauma script driven imagery supports this idea (Rauch et al 1996). Dissociative symptoms are commonly seen in traumatized adults and children (Putnam 1997). Dissociative symptoms are defined as disruptions in the usually integrated functions of consciousness, memory, identity, or perception of the environment that interferes with the associative integration of information (Putnam 1997). Our finding of negative correlations with the Child Dissociative Checklist score and total corpus callosum area is intriguing. One wonders whether dissociative symptoms are the results of early neuron loss in the parietal and temporal cortical regions of the brain, areas that correspond to middle and posterior regions (5, 6, & 7) of the corpus callosum. We did not find a decrease in specific regions (regions 1 and 3 of the corpus callosum) corresponding to the orbital prefrontal and inferior prefrontal cortex. Because the prefrontal cortex continues to develop into the third decade of life, this finding may be evidence for cortical plasticity. We did find a trend for a decrease in the genu (regions 2), an area that reflects axons from the prefrontal cortex in maltreated subjects with PTSD. The prefrontal cortex subserves executive cognitive functions such as planned behaviors (Fuster 1980), working memory (Goldman-Rakic 1994), motivation (Weinberger 1987), and discriminating between internally and externalizing derived models of the world (Knight et al 1995); hypothesized neuron loss in this area may therefore be responsible for the many psychosocial, cognitive and behavior problems as well as much of the co-morbid psychopathology seen in child and adult survivors of childhood maltreatment. Because we did not study maltreated children without PTSD and because we do not know if these findings were present in our maltreated children before the onset of PTSD or whether it was a consequence of PTSD, these ideas must be viewed as speculative.

In this study of childhood PTSD secondary to maltreatment, we did not find the predicted decrease in hippocampal volume. Rather there was a trend toward an increase (or rather, proportionally less decrease) in the left hippocampal gray matter. Limbic structures such as the hippocampus are the principal neural target tissue of glucocorticoids (McEwen et al 1992; Sapolsky and Pulsinelli 1985). In a related study, we found elevated baseline 24-hour urinary free cortisol and catecholamine concentrations in maltreated prepubertal children with a diagnosis of PTSD compared to healthy non-abused controls (also see Part I of this paper [De Bellis et al 1999]). Smaller hippocampal volumes were reported in adults with Cushing's Syndrome (Starkman et al 1992), combat veterans with PTSD (Bremner et al 1995) (Gurvits et al 1996), adult 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 investigations, like our maltreated child and adolescent PTSD subjects, 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. Our subjects did have less co-morbid histories of alcohol and substance abuse as only four of our adolescent subjects had this history. High levels of alcohol are known to be associated with hippocampal damage in rats (Bengoechea and Gonzalo 1991) and humans (Sullivan et al 1995), and cocaine, another commonly abused substance in adult PTSD patients, can theoretically cause high levels of circulating catecholamines, and be potentially neurotoxic to the limbic areas of the brain via free radical formation (Smythies 1997); co-morbid substance abuse may account for the differences in hippocampal findings between children and adults with PTSD. Another possible explanation for the differences in hippocampal findings between children and adults with PTSD is neurodevelopmental plasticity; subcortical grey matter structures that include the limbic system (septal area, hippocampus, amygdala) actually show an increase in volume until the third decade of life (Jernigan and Sowell 1997). This increase may "mask" any effects of traumatic stress in maltreated children with PTSD. A third possible reason for the differences in hippocampal findings between children and adults with PTSD is the differences in methods used in these studies. Only one study of adult PTSD measured total brain or intracranial volume and found non-significantly smaller brains in PTSD subjects (Gurvits et al 1996). The other 4 studies, estimated intracranial volume by area measurements, which may have influenced their results. Thus more research on the brain development of chronically stressed children is needed to understand the complex interactions between brain maturation, stress, and psychobiology.

Taken together, data in Part I and Part II of our papers suggest that the overwhelming stress of maltreatment experiences in childhood is associated with alterations of biological stress systems and with adverse influences on brain development. PTSD in maltreated children and adolescents is also associated with increased psychiatric morbidity and poor psychosocial outcomes. An important mission for the field of developmental traumatology research is to unravel the complex interaction between an individual's genetic constitution, unique psychosocial environment, and proposed critical periods of vulnerability for and resilience to abusive experiences, and how such factors may influence changes in biological stress systems, adverse brain development, and

psychopathology seen. In our cross-sectional studies, we could not establish causal relationships between abuse, psychiatric symptoms, and biological changes. Caring for children who have suffered prior maltreatment offers unique challenges. Prospective longitudinal studies on the psychobiology of maltreated and at risk children are clearly needed to better clarify such cause-effect relationships. Studies of the psychobiological effects of psychotherapeutic and psychopharmacological interventions are also needed as early interventions may theoretically attenuate these changes. Elucidating the biological sequelae and mechanisms of symptom production in PTSD and associated co-morbid psychiatric disorders will clearly pave the way to better clinical and social treatment of maltreated children in the future.

This work was supported mainly by the 1995 NARSAD Young Investigators Award, "Attention and Concentration in Maltreated Children with Posttraumatic Stress Disorder" (Principal Investigator: Michael D. De Bellis, M.D.), and in parts by NIMH Grant # MH 41712 "The Psychobiology of Depression in Children & Adolescents" (Principal Investigator: Neal D. Ryan, M.D.), NIMH grants MH01180 and MH43687 (Matcheri S. Keshavan, M.D.), NIAAA grant AA08746-08 "Adolescent Alcohol Abuse: Biobehavioral Manifestations" and by NIMH grants 5 K08 MHO1324-02 (Principal Investigator: Michael D. De Bellis, M.D.) and 5 T32 MH18951 (Clinical Research Training for Dr. De Bellis). The primary author thanks Frank W. Putnam, Jr., M.D., Director of the Unit on Developmental Traumatology at the NIMH and one of the founders of Developmental Traumatology Research for his invaluable mentorship throughout the years and the following staff of the Developmental Traumatology Laboratory: Jennifer Apicella, Clayton H. Eccard, Adam Kersh, Grace Moritz, M.S.W., and Cara Renzelli, M.S.Ed., Ester Saghafi, Med, MLS of the WPIC Health Sciences Library System, and A. Catherine Vaituzis of the Child Psychiatry Branch of the NIMH, and Sati Mazumdar, Ph.D., and Satish Iyengar, Ph.D., for their statistical consultations; the staff of Family Resources and The Whale's Tale, two non-profit community mental health clinics that serve maltreated children and their families for the clinical care of these maltreated subjects; the parents and children who participated in this study; and David Kupfer, M.D., and David Brent, M.D. for their support of this work.

References

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

Alexander GE, Goldman PS (1978): Functional development of the dorsolateral prefrontal cortex: an analysis utilizing reversible cryogenic depression. *Brain Res* 143:233–249.

Andreasen NC, Flaum M, Swayze II V, et al (1993): Intelligence and brain structures in normal individuals. *Am J Psychiatry* 150:130–134.

Atkinson L, Bowman TG, Dickens S, et al (1990): Stability of Wechsler Adult Intelligence Scale-Revised factor scores across time. *Psychol Assess* 2:447–450.

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

Azar ST, Barnes KT, Twentyman CT (1988): Developmental outcomes in abused children: consequences of parental abuse or a more general breakdown in caregiver behavior? *Behav Ther* 11:27–32.

Bengoechea O, Gonzalo LM (1991): Effects of alcoholization on rat hippocampus. *Neuroscience Lett* 123:112–114.

Blinkov SM, Glezer II (1968): *The Human Brain in Figures and Tables: A Quantitative Handbook*. New York: Plenum.

Boulanger G (1985): Post-traumatic stress disorder: An old problem with a new name. In: Sonnenberg SM, Blank AS, Talbott JA, editors. *The Trauma of War: Stress and Recovery in Vietnam Veterans*. Washington, DC: American Psychiatric Press, pp 13–29.

Bremner JD, Randall P, Scott TM, et al (1995): MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry* 152:973–981.

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

Bremner JD, Scott TM, Delaney RC, et al (1993a): Deficits in short-term memory in post-traumatic stress disorder. *Am J Psychiatry* 150:1015–1019.

Bremner JD, Southwick SM, Johnson DR, Yehuda R, Charney DS (1993b): Childhood physical abuse and combat-related posttraumatic stress disorder in Vietnam Veterans. *Am J Psychiatry* 150:235–239.

Carmichael A (1990): Physical development and biological influences. In: Tonge B, Burrows GD, Werry JS, editors. *Handbook of Studies in Child Psychiatry*. Amsterdam: Elsevier.

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.

Chambers WJ, Puig-Antich J, Hirsch M, et al (1985): The assessment of affective disorders in children and adolescents by semi-structured interview: test-retest reliability of the schedule for affective disorders and schizophrenia for school-age children, present episode version. *Arch Gen Psychiatry* 42:696–702.

Cicchetti D, Lynch M (1995): Failures in the expectable environment and their impact on individual development: the case of child maltreatment. In: Cicchetti D, Cohen DJ, editors. *Developmental Psychopathology, Vol. 2*. New York: John Wiley & Sons Inc., pp 32–71.

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, Inc., pp 455–494.

De Bellis MD, Baum A, Birmaher B, et al (1999): Developmental traumatology part I: Biological stress systems. *Biol Psychiatry* 45:1259–1270.

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

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

De Bellis MD, Putnam FW (1994): The psychobiology of

childhood maltreatment. In: Child and Adolescent Psychiatric Clinics of North America 3:663–677.

de Lacoste MC, Kirkpatrick JB, Ross ED (1985): Topography of the human corpus callosum. *J. Neuropathol Exp Neurology* 44:578–591.

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

Diamond MC, Krech D, Rosenzweig MR (1964): The effects of an enriched environment on the histology of the rat cerebral cortex. *J Comp Neurol* 123:111–120.

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

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

Elliot SN, Boeve K (1987): Stability of WISC-R IQS: An investigation of ethnic differences over time. *Educational and Psychological Measurement* 47:461–465.

Frazier JA, Giedd JN, Hamburger SD, et al (1996): Brain anatomic magnetic resonance imaging in childhood-onset schizophrenia. *Arch Gen Psychiatry* 53:617–624.

Fuster JM (1980): *The Prefontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe*. New York, NY: Raven Press.

Giedd JN, Castellanos FX, Casey BJ, et al (1994): Quantitative morphology of the corpus callosum in attention deficit hyperactivity disorder. *Am J Psychiatry* 151:665–669.

Giedd JN, Snell JW, Lange N, et al (1996a): Quantitative magnetic resonance imaging of human brain development: ages 4–18. *Cerebral Cortex* 6:551–560.

Giedd JN, Vaituzis AC, Hamburger SD, et al (1996b): Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: ages 4–18. *J Comp Neurol* 366:223–230.

Goldfeld AE, Mollica RF, Pesavento BH, Faraone SV (1988): The physical and psychological effects of torture: symptomatology and diagnosis. *JAMA* 259:2725–2729.

Goldman PS (1971): Functional development of the prefrontal cortex in early life and the problem of neuronal plasticity. *Exp Neurol* 66:366–387.

Goldman-Rakic PS (1994): Working memory dysfunction in schizophrenia. *J Neuropsychiatry Clin Neurosci* 6:348–357.

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

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

Hollingshead AB (1975): Four factor index of social status. Hollingshead, PO Box 1965, Yale Station, New Haven CT 06520.

Innocenti GM, Manzoni T, Spidalieri G (1974): Patterns of the somesthetic messages transferred through the corpus callosum. *Exp Brain Res* 19:447–466.

Jacobson M (1991): *Developmental Neurobiology*. New York: Plenum.

Jernigan T (1986): Anatomical and CT scan studies of psychiatric disorders. In: Berger P, Brodie HKH, editors. *American Handbook of Psychiatry, Vol. 8*. New York: Basic Books, pp 213–235.

Jernigan TL, Sowell ER (1997): Magnetic resonance imaging studies of the developing brain. In: Keshavan MS, Murray RM, editors. *Neurodevelopment & Adult Psychopathology*. United Kingdom: Cambridge University Press, pp 63–70.

Kaufman J (1991): Depressive disorders in maltreated children. *J Am Acad Child Adolescent Psychiatry* 30:257–265.

Kaufman J, Birmaher B, Brent D, 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 Adolescent Psychiatry* 36:980–988.

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

Keshavan MS, Beckwith C, Bagwell W, Pettegrew JW, Krishnan KR (1994): An objective method for edge detection in MRI morphometry. *Eur Psychiatry* 9:205–207.

Knight RT, Grabowecky MF, Scabini D (1995): Role of human prefrontal cortex in attention control. *Adv Neurol* 66:21–34.

Kolko D (1992): Characteristics of child victims of physical violence: research findings and clinical implications. *J Interpersonal Violence* 7:244–276.

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

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

Lezak M (1995): *Neuropsychological Assessment* (*3rd Ed.*). New York: Oxford.

Macklin ML, Metzger LJ, Litz BT, et al (1998): Lower precombat intelligence is a risk factor for posttraumatic stress disorder. *J Consult Clin Psychology* 66:232–236.

McEwen BS, Gould EA, Sakai RR (1992): The vulnerability of the hippocampus to protective and destructive effects of glucocorticoids in relation to stress. *Br J Psychiatry* 160:18–24.

McNally RJ, Shin LM (1995): Association of intelligence with severity of posttraumatic stress disorder symptoms in Vietnam combat veterans. *Am J Psychiatry* 152:936–938.

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

National Research Council (1993): *Understanding Child Abuse and Neglect*. Washington, DC: National Academy Press.

Orvaschel H, Puig-Antich (1987): Schedule for affective disorder and schizophrenia for school-age children, epidemiologic version. K-SADS-E Fourth Version.

Pearlson G, Garbacz D, Breakey W, Ahn H, DePaulo J (1984): Lateral ventricular enlargement associated with persistent unemployment and negative symptoms in both schizophrenia and bipolar disorder. *Psychiatry Res* 12:1–9.

Perez C, Widom CS (1994): Childhood victimization and long-term intellectual and academic outcomes. *Child Abuse & Neglect* 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, Inc., pp 233–255.

Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO (1994): A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Arch Neurol* 34:71–75.

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.

Pitman RK, Orr SP, Lowenhagen MJ, Macklin ML, Altman B (1991): Pre-Vietnam contents of PTSD veteran' service medical and personal records. *Comp Psychiatry* 32:1–7.

Putnam FW (1997): *Dissociation in Children and Adolescents: A Developmental Perspective*. New York NY: The Guilford Press.

Putnam FW, Peterson G (1994): Further validation of the Child Dissociative Checklist: Dissociation, VII, pp 204–211.

Pynoos RS, Steinberg AM, Wraith R (1995): A developmental model of childhood traumatic stress. In: Cicchetti D, Cohen DJ, editors. *Developmental Psychopathology, Vol. 2*. New York: John Wiley & Sons Inc., pp 72–95.

Rabinowicz T (1986): The differentiated maturation of the cerebral cortex. In: Falkner F, Tanner JM, editors. *Human Growth, Vol. 2*. New York: Plenum, pp 385–410.

Ramaekers G, Njiokiktjien C (1991): The child's corpus callosum, Pediatric Behavioral Neurology, Vol. 3. Amsterdam: Suyi Publications.

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

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

Ron M (1983): The alcoholic brain: CT scan and psychological findings. *Psychol Med Monogr* Suppl 3:1–33.

Rosenberg DR, Keshavan MS, O'Hearn KM, et al (1997): Frontostriatal measurement in treatment-naive children with obsessive-compulsive disorder. *Arch Gen Psychiatry* 54:824–830.

Rosso PR (1990): Prenatal nutrition and brain growth. In: van Gelder NM, Butterworth RF, Drujan BD, editors. *Neurology and Neurobiology: Malnutrition and Infant Brain, Vol. 58*. New York, NY: Wiley-Liss, Inc, pp 25–40.

Sapolsky R, Pulsinelli W (1985): Glucoocorticoids potentiate ischemic injury to neurons: therapeutic implications. *Science* 229:1397–1400.

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

Scott M, Golden C, Ruedrich S, Bishop R (1983): Ventricular enlargement in major depression. *Psychiatry Res* 8:91–93.

Shaffer D, Gould MS, Brasic J, et al (1983): A children's Global Assessment Scale. *Arch Gen Psychiatry* 40:1228–1231.

Shields AM, Cicchetti D, Ryan R (1994): The development of emotional and behavioral self-regulation and social competence among maltreated school-age children. *Dev Psychopathol* 6:57–75.

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.

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

Starkman MN, Gebarksi SS, Berent S, Schteingart DE (1992): Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. *Biol Psychiatry* 32:756–765.

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.

Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A (1995): Anterior hippocampal volume deficits in non-amnesiac, aging chronic alcoholics. *Alcohol Clin Exp Res* 19:110–122.

Sutker PB, Winstead DK, Galina ZH, Allain AN (1990): Trauma-induced weight loss and cognitive deficits among former POW survivors of the Korean Conflict. *J Personal Assess* 54:170–180.

Sutker PB, Winstead DK, Galina ZH, Allain AN (1991): Cognitive deficits and psychopathology among former prisoners of war and combat veterans of the Korean Conflict. *Am J Psychiatry* 148:67–72.

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 RM, editor. *Psychobiology of Posttraumatic Stress Disorder, Vol 821*. New York NY: Annals of the New York Academy of Sciences, pp 160–175.

Todd RD (1992): Neural development is regulated by classical neuro-transmitters: dopamine D_2 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.

Uno H, Tarara R, Else J, Suleman MA, Sapolsky RM (1989): Hippocampal damage associated with prolonged and fatal stress in primates. *J Neurosci* 9:1705–1711.

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

Weinberger DR (1987): Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 44:660–669.

Weinberger DR, Wyatt RJ (1982): Cerebral ventricular size: a biological marker for subtyping chronic schizophrenia. In: Usdin E, Handen J, editors. *Biological Markers in Psychiatry and Neurology*. Elmford, NY: Pergamon Press, pp 505–512.

Werry JS (1991): Brain and behavior. In: Lewis M, editor. *Child and Adolescent Psychiatry: A Comprehensive Textbook, 2nd Edition*. Baltimore, MD: Williams & Wilkins, pp 86–96.

Witelson SF (1989): Hand and sex differences in the isthmus and genu of the human corpus callosum. *Brain* 112:799–835.

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