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Sex differences in brain maturation in maltreatment-related pediatric posttraumatic stress disorder

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Abstract

Background. Recent investigations suggested that pediatric posttraumatic stress disorder (PTSD) is associated with adverse brain development. However, sex differences are poorly understood.

Methods. In this study, 61 medically healthy children and adolescents (31 males and 30 females) with chronic PTSD secondary to abuse, who had similar trauma and mental health histories, and 122 healthy controls (62 males and 60 females) underwent comprehensive psychiatric assessments and an anatomical MRI brain scan.

Results. When gender groups were analyzed separately, findings of larger prefrontal lobe CSF volumes and smaller midsagittal area of the corpus callosum subregion 7 (splenium) were seen in both boys and girls with maltreatment-related PTSD compared to their gender-matched comparison subjects. Subjects with PTSD did not show the normal age related increases in the area of the total corpus callosum and its region 7 (splenium) compared to non-maltreated subjects; however, this finding was more prominent in males with PTSD. Significant sex by group effects demonstrated smaller cerebral volumes and corpus callosum regions 1 (rostrum) and 6 (isthmus) in PTSD males and greater lateral ventricular volume increases in maltreated males with PTSD than maltreated females with PTSD.

Conclusions. These data suggest that there are sex differences in the brain maturation of boys and girls with maltreatment-related PTSD. Longitudinal MRI brain investigations of childhood PTSD and the relationship of gender to psychosocial outcomes are warranted.

Keywords: Posttraumatic stress disorder; Child abuse; Maltreatment; Sex differences; Brain development; Cerebral volumes; Lateral ventricles; Corpus callosum; Developmental traumatology; Early adverse experience

1. Introduction

Maltreatment of children, defined as neglect, physical abuse, sexual abuse, and emotional abuse (which includes witnessing domestic violence) is both a cause and a risk factor for the diagnosis of posttraumatic stress disorder (PTSD) and a common contributor to child and adult mental illness [1,2]. Childhood trauma may have psychopathological (signs and symptoms of PTSD) and developmental consequences [3,4], including adverse emotional [5–7], behavioral [5], and cognitive consequences [8]. PTSD is commonly seen in maltreated children, especially during the period immediately following maltreatment disclosure [9,10]. PTSD is a debilitating chronic mental illness with enormous social and economic costs [11]. The diagnosis of PTSD is made when criterion A, exposure to an extreme traumatic stressor in which the person responded with intense fear, helplessness, horror or, in children, disorganized or agitated behaviors, is experienced and when three clusters of categorical symptoms, intrusive reexperiencing of the trauma(s) (criterion B), persistent avoidance of stimuli associated with the trauma(s) (criterion C), and persistent symptoms of increased physiological arousal (criterion D), are present for more than 1 month after the traumatic event(s) [12].

PTSD is an anxiety disorder. Children are more vulnerable to developing PTSD after experiencing trauma than their adult counterparts [13]. Maltreated children and adolescents manifest high rates of PTSD symptoms, depression, suicidal thoughts and behaviors, aggression

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and antisocial behaviors, and cognitive deficits [14]. Furthermore, subdisorder level PTSD symptoms are commonly seen in victims of childhood maltreatment. Even children with subdisorder level PTSD symptoms have substantial functional impairment and distress [15]. The causes of these high rates of anxiety and mood disorders in maltreated children are both familial/genetic and environmental. Increased rates of mood and anxiety disorders are found in parents involved in their children's maltreatment [16]. However, environmental factors also play an important contributing role. A study of twins discordant for child abuse exposure demonstrated that the twin exposed to abuse suffered from an increased risk for adult psychopathology compared to the non-exposed twin [17].

Maltreated children develop under the psychobiological influence of chronic stress. Maltreated children with and without PTSD demonstrate dysregulation of biological stress response systems at baseline and during experimental challenges compared to non-maltreated individuals [14]. These neurobiological differences likely contribute to psychopathology. Birth to adulthood is marked by progressive physical, behavioral, cognitive, and emotional development that parallel changes in brain maturation. Although these processes are influenced strongly by genetics, positive and negative environmental experiences also play an important role. 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 [18–21], delays in myelination [22], abnormalities in developmentally appropriate pruning [23,24], and/or the inhibition of neurogenesis [25–27]. Furthermore, stress decreases brain-derived neurotrophic factor expression [28]. Thus, the chronic stress of child maltreatment experiences may have adverse influences on a child's brain development.

Childhood brain development is characterized by regressive and progressive processes, such as synaptic and axonal pruning [29] and progressive myelination [30]. Magnetic resonance imaging (MRI) provides a non-invasive method to examine differences in brain maturation between maltreated and non-maltreated and healthy normally developing children. Findings from cross-sectional studies of healthy childhood brain development suggest that the proportion of cerebral grey matter, which reflects the somatodendritic tissue of cortical and subcortical neurons, to white matter, which reflects the axonal compartment of myelinated connecting fibers, decreases progressively after age 4 [31]. Results from longitudinal studies demonstrated that there are regionally specific nonlinear pre-adolescent increases followed by post-adolescent decreases in cortical grey matter [32,33]. Increases in myelination, reflected by corpus callosum area, the main interhemispheric commissure, continue into the third decade [32,34,35]. Recent findings from longitudinal MRI studies of healthy children and adolescents have confirmed these age-related progressive changes in axonal growth and myelination [32,33,35]. Sex steroids influence neurodevelopment throughout the life span [36]. However, brain maturational sex differences are an understudied area in humans. In one pediatric neuroimaging study of healthy children and adolescents, boys showed significantly greater loss of grey matter volume and an increase in both white matter and corpus callosum area as compared to girls, over a similar age range; suggesting sex differences in both cerebral grey and white matter maturational processes in childhood and adolescence [37]. In another study of healthy adults, age 18–45 years, similar sex differences were also seen [38].

Unlike findings in adult PTSD where several studies reported hippocampal atrophy [39], MRI studies of maltreated children suggest that child abuse-related PTSD is associated with global adverse brain development. In one research study, 43 maltreated children and adolescents with PTSD and 61 matched controls underwent comprehensive clinical assessments and an anatomical MRI brain scan [40]. Maltreated subjects with PTSD had 7.0% smaller intracranial and 8.0% smaller cerebral volumes than controls. The total midsaggital area of corpus callosum, and the middle and posterior regions of the corpus callosum, were smaller in abused subjects. In contrast, right, left, and total lateral ventricles and prefrontal cortical cerebral spinal fluid (CSF) were proportionally larger than controls, after adjustment for intracranial volume. In another study from our group which controlled for socioeconomic status, 28 psychotropic-naïve children and adolescents with abuse-related PTSD and 66 sociodemographically similar healthy controls underwent comprehensive clinical assessments and anatomical MRI brain scans [41]. Compared with controls, 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 (2,4–7), and larger frontal lobe CSF volumes than controls. The total midsagittal area of corpus callosum and middle and posterior regions remained smaller, while right, left, and total lateral ventricles and frontal lobe CSF were proportionally larger than controls, after adjustment for cerebral volume. In these two studies, the finding of positive correlations of intracranial and cerebral volumes with age of onset of PTSD trauma suggest that traumatic stress is associated with disproportionately negative consequences if it occurs during early childhood. The finding of negative correlations of intracranial and cerebral volumes with abuse duration suggest that childhood maltreatment has global and adverse influences on brain development that may be cumulative. In another study from a separate research group, smaller brain and cerebral volumes were also seen in maltreated children with subthreshold PTSD and threshold PTSD compared with archival controls [42]. Interestingly, maltreated children and adolescents with PTSD or subthreshold PTSD showed no anatomical differences in limbic (hippocampal or amygdala) structures cross-sectionally [40–42] or longitudinally [43]. Furthermore, findings in pediatric PTSD differ from those

of children and adolescents who have no history of criterion A trauma and who suffer from generalized anxiety disorder. These children may have an inherent dysmorphometry of the neurobiologic structures implicated in fear and anxiety. Children with generalized anxiety disorder have larger and particularly right sided amygdala [44] and superior temporal gyrus [45] volumes. Thus, traumatic stress during childhood may be associated with disproportionately negative effects on brain maturation.

Although cognitive and emotional development differs between boys and girls [46,47], the effects of maltreatment-related PTSD between genders and the neurobiological parallels of such differential development remain poorly understood. In our two previously published studies, 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 [40]. In the more recent study, a significant sex by group effect demonstrated greater lateral ventricular volume increases in maltreated males with PTSD than maltreated females with PTSD [41]. These findings may suggest that males are more vulnerable to the effects of severe stress in global brain structures than females. However, in the few studies published to date, sex differences are relatively small compared to the known developmental variability in volume of brain structures. Consequently, relatively large samples of boys and girls are needed to carefully examine this issue. Therefore, we investigated the relationship between intracranial, cerebral, prefrontal cortex, and lateral ventricle volumes, and corpus callosum area in relation to age and sex using high resolution MRI volumetric analyses in a relatively large and gender matched sample of maltreated children and adolescents with PTSD and healthy non-maltreated controls. Subjects were pooled from our previously described studies [40,41] in order to have a large enough sample size of boys and girls to examine sex differences between groups. PTSD subjects and control subjects were selected from these studies if they were psychotropic-naïve and had no significant history of prenatal substance exposure, adolescent onset substance abuse, and were medically and neurologically healthy prior to their MRI scan. Furthermore, in this sample, boys and girls with maltreatment-related PTSD suffered from similar traumas and had similar histories of co-morbid mental illness, behavioral problems and cognitive deficits. In this study, we specifically investigated age-related sex differences in the developmental brain maturational processes of boys and girls who had similar trauma and mental health histories. In this way, sex differences in brain maturation could be examined that may be related to an inherent vulnerability of boys versus girls to chronic and severe stress but may possibly be unrelated to having an anxiety disorder.

2. Subjects and methods

2.1. Subjects

Sixty-one psychotropic-naïve maltreated children and adolescents with DSM-IV chronic PTSD, aged 4–17 years, and 122 healthy non-abused controls were recruited. Because of the high degree of known developmental variability in volume of brain structures [48], two controls were case matched for each PTSD subject for age (within 6 months) and sex. Brain measures of these subjects were previously published [40,41]. These subjects were pooled from these previously studies in order to have a large enough of a sample size to examine sex differences between groups. PTSD subjects and control subjects were selected from these studies if they were psychotropic-naïve and had no significant history of prenatal substance exposure, adolescent onset substance abuse, and were medically and neurologically healthy. Groups were similar on measures of handedness, height, weight, Tanner Stage, race, birth weight, and history of full term pregnancy. Further information by gender groups is provided (Table 1). 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 [49] (for further discussion see Ref. [40]).

2.2. Clinical assessments

Subjects and their legal guardian were evaluated by a board certified child psychiatrist (M.D.D.B.) using a detailed trauma interview as described [4] and by a trained Master's level clinician (who was blind to clinical status prior to the semi-structured interview) using a modified version of the Schedule for Affective Disorders and Schizophrenia for School-Age, Present and Lifetime versions (K-SADS-PL) [50]. For subjects who witnessed domestic violence prior to age 4 years, the diagnosis of PTSD from emotional abuse was made on more objective criteria based on behaviors observed by the caregiver and/or reported in medical records [51]. Consensus meetings were held after the structured interview (M.D.D.B. and G.M.) 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) [52] during the initial screening. Parents of subjects completed the Child Behavior Checklist (CBCL) [53], and the Child Dissociative Checklist (CDC) [54]. For further details see Refs. [40,41].

Inclusion criteria were the following. (1) A DSM-IV diagnosis of chronic PTSD that resulted from child

Table 1
Demographic characteristics of male and female maltreated children and adolescents with PTSD and non-maltreated healthy controls

	PTSD	Control	Male			Female		
			PTSD	Control	Statistic, p	PTSD	Control	Statistic, p
$N = 183$	61	122	31	62		30	60	
Age (years) (range in years)	11.74 ± 2.63 (4.9–16.5)	11.71 ± 2.56 (4.3–17.0)	12.2 ± 2.5 (7.0–16.5)	12.0 ± 2.3 (6.9–17.0)	$t_{91} = -0.38$; $p = 0.70$	11.3 ± 2.8 (4.9–15.8)	11.4 ± 2.8 (4.3–16.3)	$t_{88} = 0.21$; $p = 0.84$
Weight (kg)	46.85 ± 16.84 (15.0–101.6)	47.60 ± 17.77 (16.3–105.7)	48.62 ± 16.83 (25–101.6)	51.0 ± 18.0 (20–105.7)	$t_{91} = 0.61$; $p = 0.54$	45.03 ± 16.94 (15.0–85.3)	44.1 ± 17.0 (16.3–92.1)	$t_{88} = -0.25$; $p = 0.81$
Height (cm)	150.42 ± 16.0 (95.9–180.0)	151.56 ± 17.2 (103.0–189.2)	153.4 ± 15.1 (124.5–180.0)	155.9 ± 15.0 (121.9–189.2)	$t_{91} = 0.77$; $p = 0.44$	147.4 ± 16.6 (95.9–168.9)	147.0 ± 18.2 (103–172.7)	$t_{88} = 0.01$; $p = 0.92$
Tanner Stage (I/II/III/IV/I)	18/15/15/7/6	39/31/28/16/8	9/9/7/4/2	19/19/13/6/5	FET, ns	9/6/8/3/4	20/12/15/10/3	FET, ns
Handedness (Right/Left)	57/4	117/5	28/3	59/3	FET, ns	29/1	58/2	FET, ns
SES (range)	3.1 ± 1.1 (1–5)	3.6 ± 0.9 (1–5)	34.5 ± 11.1 (17–50.5)	41.8 ± 10.9 (18–64)	$t_{91} = 3.00$; $p < 0.004$	35.2 ± 10.6 (22–59.5)	39.2 ± 8.5 (18–58)	$t_{88} = 1.93$; $p = 0.06$
Verbal IQ (range)	105.3 ± 15.2 (74–152)	114.3 ± 13.0 (87–147)	103.4 ± 16.5 (75–152)	116.6 ± 13.9 (89–145)	$t_{91} = 4.06$; $p = 0.0001$	107.3 ± 14.5 (74–132)	112.0 ± 11.5 (87–147)	$t_{88} = 1.66$; $p = 0.1$
Performance IQ (range)	107.13 ± 18.4 (72–155)	118.0 ± 18.1 (72–152)	107.3 ± 20.0 (72–146)	117.3 ± 20.3 (72–152)	$t_{91} = 2.28$; $p < 0.03$	107.0 ± 16.9 (80–155)	118.7 ± 15.7 (81–152)	$t_{88} = 3.25$; $p = 0.001$
Fullscale IQ (range)	107.0 ± 15.1 (78–137)	117.5 ± 15.5 (78–153)	105.9 ± 16.3 (78–135)	118.5 ± 17.7 (78–153)	$t_{91} = 3.33$; $p = 0.001$	108.1 ± 14.1 (79–137)	116.5 ± 13.0 (90–145)	$t_{88} = 2.81$; $p = 0.006$

PTSD, posttraumatic stress disorder; SES, socioeconomic status; FET, Fisher's exact test.

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, prior to 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. (5) Living in a stable home environment, defined as not in danger from perpetrator(s) for a period of at least 3 months prior to this study.

All PTSD subjects had a diagnosis of DSM-IV chronic PTSD. The mean age of onset, duration of the maltreatment trauma that led to PTSD, mean length of time between maltreatment disclosure and MRI scan and type of abuse were similar for boys and girls. Sexual abuse was the most common reason for PTSD given by the subjects for both boys (26/31) and girls (23/30). Most PTSD subjects, including many of the sexually abused subjects, witnessed domestic violence (44 of 61). Some subjects (7 of 61) met DSM-IV PTSD criteria for witnessing domestic violence and sexual abuse. These cases involved the same perpetrator (i.e. natural father or mother's paramour). Since the abusive experiences overlapped in time, they were coded as one traumatic event with PTSD from witnessing domestic violence as the onset and disclosure of sexual abuse as the offset of trauma. Information was obtained from caregiver(s), and from review of Child Protective Service or other available medical/psychiatric records. Fifty-three of the PTSD subjects had co-morbid psychiatric disorders. Forty-three of the 61 PTSD subjects met criteria for three or more DSM-IV axis I diagnoses. These disorders were similar between boys and girls. Males and females with PTSD were also similar in terms of the number of PTSD cluster B (intrusive), cluster D (hyperarousal), depressive and CBCL internalizing and externalizing symptoms and in histories of suicidal ideation and attempts. Males with PTSD showed a trend to report more cluster C (numbing, depersonalization and dissociative) symptoms than females with PTSD (Table 2). MRI structural volumes and corpus callosum area data on subjects were previously reported in Refs. [40,41].

Exclusion criteria were: (1) significant medical illness or birth complications or history of head trauma with loss of consciousness; (2) gross obesity or growth failure; (3) full

Table 2
Abuse and clinical characteristics of male and female maltreated children and adolescents with PTSD

Variable (SD)	Males with PTSD	Females with PTSD	Statistic	p
Age of abuse onset (years)	4.29 ± 2.44	3.44 ± 2.38	$t_{1,59} = 1.37$	0.18
Duration of abuse (years)	3.92 ± 2.56	4.38 ± 1.67	$t_{1,59} = 0.83$	0.41
Duration since disclosure (years)	3.94 ± 2.88	3.50 ± 2.49	$t_{1,59} = 0.64$	0.52
Causes of PTSD				
Sexual abuse	24	18	$X2 = 2.16$	0.14
Physical abuse	3	2	FET	ns
Emotional abuse (i.e. witnessing domestic violence)	7	12	$X2 = 2.16$	0.14
Sexual abuse and emotional abuse	2	5	FET	ns
Characteristics of multiple maltreatments				
Number with sexual abuse	24	18	$X2 = 2.16$	0.14
Number with physical abuse	18	13	$X2 = 1.32$	0.25
Number with emotional abuse (i.e. witnessing domestic violence)	22	22	$X2 = 0.04$	0.84
Number of PTSD cluster B symptoms	2.13 ± 1.23	2.10 ± 1.12	$Z = 0.02$	0.98
Number of PTSD cluster C symptoms	4.13 ± 1.06	3.67 ± 1.09	$Z = 1.71$	0.09
Number of PTSD cluster D symptoms	3.26 ± 0.86	3.00 ± 0.79	$Z = 1.28$	0.20
Child depression inventory score	9.19 ± 6.77	11.93 ± 9.83	$Z = 1.03$	0.30
CDC score	11.77 ± 6.19	8.20 ± 5.07	$Z = 1.59$	0.11
History of suicidal ideation	25	22	$X2 = 0.46$	0.50
History of suicide attempts	8	9	$X2 = 0.13$	0.72
Co-morbidity				
Mean number of axis I disorders	3.00 ± 1.09	3.10 ± 1.16	$Z = 0.52$	0.61
Number with dysthymia	21	20	$X2 = 0.01$	0.93
Number with major depression	14	17	$X2 = 0.81$	0.37
Number with oppositional defiant disorder	12	14	$X2 = 0.40$	0.53
Number with attention deficit hyperactivity disorder	13	8	$X2 = 1.58$	0.21
Number with separation anxiety disorder	2	4	FET	0.42
CBCL total T score	65.52 ± 11.43	64.10 ± 13.21	$Z = 0.50$	0.62
CBCL internalizing symptoms T score	63.06 ± 12.05	61.70 ± 11.57	$t_{59} = 0.45$	0.65
CBCL externalizing symptoms T score	64.58 ± 11.54	63.53 ± 14.88	$Z = 0.07$	0.94

PTSD, posttraumatic stress disorder; SES, socioeconomic status; FET, Fisher's exact test Z, Wilcoxon/Kruskal-Wallis sum rank tests.

scale IQ <70; (4) anorexia nervosa, pervasive developmental disorder, schizophrenia or adolescent onset alcohol or substance abuse or dependence; (5) prenatal exposure of either alcohol and/or other substance use on a greater than two times a month basis during the first 3 months (prior to discovery) of pregnancy and any prenatal substance exposure during a known pregnancy with the subject. (6) Any contraindication for MRI scans (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 was consented to participate independently of a parent or legal guardian. Subjects received monetary compensation for participation.

2.3. MRI image analysis

For complete description of MRI scans and image analysis see Refs. [40,41]. The imaging data were analyzed using IMAGE software (version 1.52) [55]. All measurements were made by trained and reliable raters who were blind to subject information (J.H. and K.F., J.H. and A.M.B., or J.H. and J.N.). 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, and cerebral grey and white matter (J.H. and K.F.) and prefrontal cortex (J.H. and A.M.B.). Intrarater and interrater reliability from 20 subjects ranged from 0.93 to 0.99 and 0.90 to 0.99, respectively, for total corpus callosum area and subdivisions (J.H. and A.M.B and J.H. and J.N.) and were 0.97 and 0.98, respectively, for lateral ventricles (S.K. and A.K). These methods were previously described [40,41], are available on request, and briefly described later.

Intracranial volumes were calculated by first manually tracing the intracranial volume of each coronal slice after exclusion of skull and dura, then summing these areas of successive coronal slices and multiplying by slice thickness. These measures included frontal, parietal, temporal, occipital cortex, subcortical structures, cerebellum and brainstem. Cerebral volumes were measured after manual exclusion of CSF volumes, cerebellum and brainstem in the same manner and included cortical and subcortical structures. Total cerebral grey matter and white matter volumes were calculated using a semiautomated segmentation algorithm. This computerized segmentation technique is manually operated. It uses an interactive method using mathematically derived cutoffs for grey matter–white matter–CSF partitions from histograms of signal intensities to select grey matter, white matter, and CSF areas from each coronal slice. Grey matter and white matter and CSF areas are thus individually accessed and multiplied by slice thickness for individual subjects' grey matter, white matter, and CSF volumes. In this way, we can minimize the inherent limitations on qualifying white matter signal hypointensities as grey matter on T1-weighted MRI scans by visual inspection of slices. This approach has been validated using both a stereology technique for brain morphometric measurements and a phantom with known absolute volumes [56] and has been used in several published neuroimaging studies [40,57,58]. Total cerebral grey matter and white matter volume measures included cortical and subcortical white and grey matter volumes.

Prefrontal cortex volumes were calculated by summing up areas of successive coronal slices, including grey and white matter and 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 [58].

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 in order to more reliably exclude the choroid plexus.

The corpus callosum area was measured from a single midsagittal section selected as the slice showing full visualization of the anterior and posterior commissures and the cerebral aqueduct. Perpendiculars were drawn to divide this area into seven regions (rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus, and splenium) [40].

2.4. Data analysis

Demographic variables were compared using Student's *t*-test, Pearson chi square, Fisher 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 examine any outlying observations. For each gender group, 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 comparison subjects. More involved regression analyses were undertaken within each gender group to test differences between PTSD and comparison subjects adjusting for cerebral volume, age and age by group interactions and to examine the influence of demographic and clinical variables (i.e. SES and verbal IQ scores) on brain structures. In testing for group differences in the normal right–left structural asymmetry of the lateral ventricles, 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 differing significantly between PTSD and comparison subjects within each gender group were correlated with clinical data using Pearson's or Spearman correlations because of the non-normal distribution of clinical measures. All significance testing was two-tailed with alpha = 0.05. All data are presented as mean ± standard deviation (SD) unless otherwise specified.

3. Results

3.1. Overall structural comparisons between PTSD subjects and controls

Overall structural differences between maltreated subjects with PTSD and comparison subjects were reported in previous studies [40,41] and are only provided here for the sake of completeness (Table 3). Linear regression analyses are provided for analyses undertaken to test differences between PTSD and comparison subjects, adjusting for cerebral volume, sex and sex by group interactions and to contrast the separate group analyses for each gender group undertaken later. As found in our previous studies, maltreated children and adolescents with PTSD had smaller intracranial and cerebral volumes and smaller total midsagittal area of corpus callosum and its regions 2 (genu), 4 (anterior midbody), 5 (posterior midbody), 6 (isthmus) and 7 (splenium) than comparison subjects; while right, left, and total lateral ventricles and frontal lobe CSF were proportionally larger than controls, after adjustment for cerebral volume. Similar results were seen when SES, Verbal IQ, history of ADHD was used as a covariate.

Sex by group effects suggested that there were sex differences in brain maturation in traumatized children. Significant sex by group effects demonstrated smaller cerebral volumes and corpus callosum regions 1 (rostrum) and 6 (isthmus) in PTSD males and greater lateral ventricular volume increases in maltreated males with PTSD than maltreated females with PTSD. Since boys and girls with maltreatment-related PTSD suffered from similar traumas and had similar histories of co-morbid mental illness, behavioral problems and cognitive deficits, group differences were examined within each gender group to study sex differences in brain maturation may be related to an inherent vulnerability of young males to severe stress but may possibly be unrelated to having an anxiety disorder.

3.2. Relationship between brain structures and sex

When gender groups were analyzed separately, only the findings of larger prefrontal lobe CSF volumes and smaller midsagittal area of the corpus callosum subregions 7 (splenium) were seen in both boys and girls with maltreatment-related PTSD compared to their gender-matched comparison subjects.

Overall, maltreated males with PTSD showed more evidence of adverse brain development than maltreated females with PTSD. Maltreated males with PTSD had significantly smaller intracranial, cerebral and prefrontal grey matter volumes and smaller total midsagittal area of corpus callosum and its subregions 4 (anterior midbody), 5 (posterior midbody), and 6 (isthmus) than comparison males; while right, left, and total lateral ventricle volumes were proportionally larger than comparison males, after adjustment for cerebral volume. Interestingly, maltreated males with PTSD showed a trend to have smaller frontal lobe white matter volumes compared to non-maltreated comparison males. Similar results were seen when SES, Verbal IQ or history of ADHD was examined as a covariate. Although PTSD females had smaller intracranial and midsagittal area of the corpus callosum subregion 5 (posterior midbody), significant differences were not seen when maltreated females were compared to comparison females for these measures described previously (Table 3 and Fig. 1).

In the overall sample, males demonstrated the previously reported and replicated findings of larger intracranial, cerebral, and left lateral ventricle volumes than females and the normal right > left asymmetry was seen for lateral ventricle volume measures [59].

3.3. Relationship between brain structures, sex, and age

Overall, significant age by diagnosis interactions revealed that maltreated children with PTSD showed greater increases in prefrontal CSF volume with age compared to non-maltreated subjects and did not show the normal age related increases in the area of the total corpus callosum and its region 7 (splenium) compared to non-maltreated controls (Table 3 and Fig. 2).

Separate age by group analyses within each gender group revealed that the nature of these findings differed for maltreated boy and girls with PTSD. Overall, maltreated males with PTSD showed more evidence of delayed myelination with age than maltreated females with PTSD. Significant age by group interactions revealed that maltreated males with PTSD did not show the normal age related increases in the area of the total corpus callosum and its subregions 1 (rostrum) and 7 (splenium) compared to non-maltreated controls. Pearson's correlations between age and total corpus callosum and subregions 1 (rostrum) and 7 (splenium), adjusted for cerebral volume, were mostly significant for comparison male ($r_{60} = 0.48$, $p < 0.0001$; $r_{60} = 0.38$, $p = 0.0025$; $r_{60} = 0.46$, $p = 0.0002$) and female ($r_{58} = 0.43$, $p = 0.0007$; $r_{58} = 0.17$, $p = 0.20$; $r_{58} = 0.47$, $p = 0.0002$) subjects; but not for maltreated male ($r_{29} = 0.12$, $p = 0.52$; $r_{29} = 0.04$, $p = 0.52$; $r_{29} = 0.07$, $p = 0.71$) and female ($r_{28} = 0.22$, $p = 0.23$; $r_{28} = 0.17$, $p = 0.37$;

Table 3
Global morphometric measures of male and female maltreated children and adolescents with PTSD and non-maltreated healthy controls

Structures (cm^3)	PTSD	Control	Group, t, p-value, covariate[a], $t_{180}p$-value	Group* sex[b]	Group* age[c]	Males PTSD	Means (± SD), males control	Males, group, t_{91}; p-value	Adjusted square[d], males PTSD
Intracranial volume	1412.51 (147.6)	1487.66 (158.1)	Group: $t = 3.10$; $p = 0.002$	$F_{1,179} = 3.18$; $p < 0.08$	$F_{1,179} = 1.07$; $p = 0.30$	1466.54 (145.6)	1577.98 (139.9)	$T = 3.57$; $p = 0.0006$	–
Cerebral volume	1195.58 (121.9)	1259.93 (141.9)	Group: $t = 3.03$; $p < 0.003$	$F_{1,179} = 4.48$; $p < 0.04$	$F_{1,179} = 1.08$; $p = 0.30$	1239.57 (123.2)	1341.47 (124.7)	$T = 3.73$; $p = 0.0003$	–
Cerebral grey matter	773.30 (79.21)	806.71 (97.97)	Group: $t = -0.31$; $p = 0.76$; Cerebral vol: $t = 19.43$; $p < 0.0001$	$F_{1,178} = 0.52$; $p = 0.47$	$F_{1,178} = 0.11$; $p = 0.74$	800.89 (88.67)	849.67 (96.98)	$T = 2.35$; $p = 0.02$	807.69 (123.37)
Cerebral white matter	425.30 (67.45)	453.13 (80.86)	Group: $t = 0.06$, $p = 0.95$; Cerebral vol: $t = 15.25$; $p < 0.0001$	$F_{1,178} = 1.52$; $p = 0.22$	$F_{1,178} = 0.58$; $p = 0.45$	438.68 (68.01)	491.81 (81.61)	$T = 3.12$; $p = 0.002$	431.87 (105.53)
Lateral ventricles (total)	11.30 (5.47)	10.54 (4.30)	Group: $t = -2.27$; $p = 0.02$; Cerebral vol: $t = 5.46$; $p < 0.0001$	$F_{1,178} = 5.19$; $p = 0.02$	$F_{1,178} = 0.41$; $p = 0.52$	13.31 (5.91)	11.47 (4.28)	$T = -1.71$; $p = 0.09$	15.05 (11.64)
Rightlateral ventricles	5.69 (3.18)	5.28 (2.24)	Group: $t = -2.18$; $p = 0.03$; Cerebral vol: $t = 5.08$; $p < 0.0001$	$F_{1,178} = 3.61$; $p < 0.06$	$F_{1,178} = 0.00$; $p = 0.99$	6.63 (3.36)	5.74 (2.35)	$T = -1.48$; $p = 0.14$	7.49 (6.64)
Left lateral ventricles	5.60 (2.58)	5.26 (2.34)	Group: $t = -2.06$; $p = 0.04$; Cerebral vol: $t = 5.12$; $p < 0.0001$	$F_{1,178} = 0.58$; $p < 0.02$	$F_{1,178} = 1.49$; $p = 0.22$	6.67 (2.85)	5.73 (2.25)	$T = -1.74$; $p < 0.09$	7.56 (5.63)
Frontal volume (cm^3)	169.05 (24.36)	179.47 (28.89)	Group: $t = -0.13$; $p = 0.89$; Cerebral vol: $t = 19.56$; $p < 0.0001$	$F_{1,178} = 0.03$; $p = 0.87$	$F_{1,178} = 79$; $p = 0.37$	175.26 (26.72)	191.82 (31.15)	$T = 2.53$; $p = 0.01$	177.39 (36.51)
Frontal grey Volume	117.66 (16.95)	120.48 (18.90)	Group: $t = -1.59$; $p = 0.11$; Cerebral vol: $t = 13.41$; $p < 0.0001$	$F_{1,178} = 1.12$; $p = 0.29$	$F_{1,178} = 0.12$; $p = 0.73$	121.88 (19.53)	126.44 (21.0)	$T = 1.01$; $p = 0.31$	126.42 (31.12)
Frontal white matter	51.38 (11.31)	58.98 (14.82)	Group: $t = -1.91$; $p < 0.06$; Cerebral vol: $t = 13.42$; $p < 0.0001$	$F_{1,178} = 1.32$; $p = 0.25$	$F_{1,178} = 0.87$; $p = 0.35$	53.36 (10.92)	65.38 (16.09)	$T = 3.74$; $p = 0.0003$	50.93 (15.55)
Frontal lobe CSF	9.60 (6.80)	4.18 (2.48)	Group: $t = -7.86$; $p < 0.0001$; Cerebral vol: $t = 0.90$; $p = 0.34$	$F_{1,178} = 0.42$; $p = 0.51$	$F_{1,178} = 6.49$; $p = 0.01$	9.82 (6.01)	4.07 (2.15)	$T = -5.16$; $p < 0.0001$	13.02 (11.91)
Corpus callosum (cm^2)	7.15 (1.33)	7.84 (1.15)	Group: $t = -3.05$; $p < 0.003$; Cerebral vol: $t = 2.67$; $p = 0.008$	$F_{1,178} = 2.51$; $p = 0.11$	$F_{1,178} = 4.23$; $p = 0.04$	6.99 (1.44)	8.05 (1.27)	$T = 3.61$; $p = 0.0005$	6.46 (2.81)
Region 1 rostrum	1.49 (0.35)	1.58 (0.37)	Group: $t = -0.74$; $p = 0.46$; Cerebral vol: $t = 3.19$; $p < 0.002$	$F_{1,178} = 3.74$; $p = 0.05$	$F_{1,178} = 3.13$; $p < 0.08$	1.44 (0.36)	1.65 (0.39)	$T = 2.52$; $p = 0.01$	1.35 (0.71)
Region 2 genu	0.68 (0.16)	0.74 (0.15)	Group: $t = 1.98$; $p < 0.05$; Cerebral vol: $t = 1.11$; $p = 0.27$	$F_{1,178} = -.07$; $p = 0.78$	$F_{1,178} = 0.55$; $p = 0.46$	0.69 (0.19)	0.74 (0.17)	$T = 1.38$; $p = 0.17$	0.67 (0.37)
Region 3 rostral body	0.57 (0.17)	0.61 (0.14)	Group: $t = 1.33$; $p = 0.18$; Cerebral vol: $t = 1.25$; $p = 0.21$	$F_{1,178} = 0.37$; $p = 0.54$	$F_{1,178} = 3.58$; $p < 0.06$	0.56 (0.17)	0.62 (0.16)	$T = 1.59$; $p = 0.12$	0.54 (0.34)
Region 4 anterior midbody	0.80 (0.17)	0.88 (0.16)	Group: $t = 2.82$; $p = 0.005$; Cerebral vol: $t = 2.10$; $p < 0.04$	$F_{1,178} = 1.21$; $p = 0.27$	$F_{1,178} = 3.40$; $p < 0.07$	0.78 (0.19)	0.90 (0.17)	$T = 3.08$; $p < 0.003$	0.72 (0.36)
Region 5 posterior midbody	0.71 (0.17)	0.79 (0.14)	Group: $t = 3.22$; $p < 0.002$; Cerebral vol: $t = 1.06$; $p = 0.29$	$F_{1,178} = 0.49$; $p = 0.48$	$F_{1,178} = 1.12$; $p = 0.29$	0.69 (0.17)	0.79 (0.16)	$T = 2.97$; $p < 0.004$	0.63 (0.33)
Region 6 Isthmus	0.61 (0.16)	0.70 (0.15)	Group: $t = 3.23$; $p < 0.002$; Cerebral vol: $t = 0.53$; $p = 0.59$	$F_{1,178} = 5.59$; $p < 0.02$	$F_{1,178} = 0.004$; $p = 0.95$	0.58 (0.16)	0.72 (0.16)	$T = 4.07$; $p < 0.0001$	0.49 (0.33)
Region 7 splenium	1.99 (0.41)	2.23 (0.35)	Group: $t = 3.55$; $p < 0.0005$ Cerebral vol: $t = 2.87$; $p < 0.005$	$F_{1,178} = 0.85$; $p = 0.36$	$F_{1,178} = 4.41$; $p < 0.03$	1.97 (0.45)	2.29 (0.37)	$T = 3.62$; $p = 0.0005$	1.81 (0.88)

[a] Linear regression adjusting for group and cerebral volume.
[b] Linear regression adjusting for group, sex, group by sex interaction and cerebral volume.
[c] Linear regression adjusting for group, age, group by age interaction and cerebral volume.
[d] Means are adjusted for cerebral volume.

Least means (± SD), males control	Group, t; p-value, covariate[a], t_{90}; p-value	Males group*age[c], statistic[d], p	Females means (± SD), PTSD	Females control	Females, group, t_{88}; p-value	Adjusted square[d], females PTSD	Least means (± SD), female controls	Group, t; p-value, covariate[a], t_{87}; p-value	Females group*age[c], statistic[d], p
–	–	$F_{1,89} = 2.45$, $p = 0.12$	1356.68 (129.62)	1394.34 (116.46)	$T = 1.39$; $p = 0.17$	–	–	–	$F_{1,86} = 0.001$, $p = 0.98$
–	–	$F_{1,89} = 1.89$, $p = 0.17$	1150.12 (104.18)	1175.67 (104.82)	$T = 1.09$; $p = 0.28$	–	–	–	$F_{1,86} = 0.02$, $p = 0.90$
846.26 (147.11)	Group: $t = -0.84$; zz$p = 0.40$; Cerebral vol: $t = 11.93$; $p < 0.0001$	$F_{1,88} = 1.73$; $p = 0.19$	744.79 (56.48)	762.32 (77.56)	$T = 1.10$ $p = 0.27$	742.13 (89.69)	763.65 (112.62)	Group: $t = 0.40$; $p = 0.69$; Cerebral vol: $t = 11.44$; $p < 0.0001$	$F_{1,85} = 0.91$; $p = 0.34$
495.23 (136.42)	Group: $t = -0.84$; $p = 0.40$; Cerebral vol: $t = 8.14$; $p < 0.0001$	$F_{1,88} = 1.73$; $p = 0.19$	411.47 (65.10)	413.16 (57.69)	$T = 0.13$; $p = 0.90$	417.49 (97.01)	410.15 (91.03)	Group: $t = -0.99$; $p = 0.32$; Cerebral vol: $t = 10.15$; $p < 0.0001$	$F_{1,85} = 0.28$; $p = 0.60$
10.59 (8.28)	Group: $t = -2.73$; $p < 0.008$; Cerebral vol: $t = 2.94$; $p = 0.004$	$F_{1,88} = 0.51$; $p = 0.48$	9.22 (4.11)	9.59 (4.14)	$T = 0.40$; $p = 0.69$	9.20 (7.67)	9.60 (8.06)	Group: $t = -0.05$; $p = 0.96$; Cerebral vol: $t = 3.18$; $p = 0.002$	$F_{1,85} = 0.47$; $p = 0.49$
5.31 (4.58)	Group: $t = -2.36$; $p = 0.02$; Cerebral vol: $t = 2.58$; $p = 0.01$	$F_{1,88} = 0.12$; $p = 0.73$	4.73 (2.71)	4.80 (2.03)	$T = 0.15$; $p = 0.88$	4.80 (5.08)	4.77 (3.95)	Group: $t = 0.23$; $p = 0.82$; Cerebral vol: $t = 3.34$; $p = 0.001$	$F_{1,85} = 0.002$; $p = 0.96$
5.28 (4.36)	Group: $t = -2.75$; $p = 0.007$; Cerebral vol: $t = 2.92$; $p < 0.005$	$F_{1,88} = 1.05$; $p = 0.31$	4.50 (1.68)	4.79 (2.32)	$T = 0.61$; $p = 0.55$	4.40 (3.19)	4.84 (4.55)	Group: $t = 0.32$; $p = 0.75$; Cerebral vol: $t = 2.56$; $p = 0.01$	$F_{1,85} = 1.59$; $p = 0.21$
190.75 (44.14)	Group: $t = -0.93$; $p = 0.35$; Cerebral vol: $t = 14.08$; $p < 0.0001$	$F_{1,88} = 0.10$; $p = 0.76$	162.63 (20.13)	166.7 (19.57)	$T = 0.92$; $p = 0.36$	162.27 (32.44)	166.88 (29.64)	Group: $t = 0.18$; $p = 0.86$; Cerebral vol: $t = 9.97$; $p < 0.0001$	$F_{1,85} = 0.51$; $p = 0.48$
124.17 (32.73)	Group: $t = -2.39$; $p < 0.02$; Cerebral vol: $t = 10.37$; $p < 0.0001$	$F_{1,88} = 0.001$; $p = 0.98$	113.3 (12.69)	114.33 (14.18)	$T = 0.33$; $p = 0.74$	113.90 (23.27)	114.03 (23.97)	Group: $t = -0.36$; $p = 0.72$; Cerebral vol: $t = 6.62$; $p < 0.0001$	$F_{1,85} = 0.17$; $p = 0.68$
66.59 (26.95)	Group: $t = 1.60$; $p = 0.11$; Cerebral vol: $t = 8.19$; $p < 0.0001$	$F_{1,88} = 0.22$; $p = 0.64$	49.33 (11.53)	52.38 (9.77)	$T = 1.31$; $p = 0.19$	48.37 (18.96)	52.86 (16.62)	Group: $t = 0.80$; $p = 0.43$; Cerebral vol: $t = 7.48$; $p < 0.0001$	$F_{1,85} = 0.38$; $p = 0.54$
2.47 (4.46)	Group: $t = -6.04$; $p < 0.0001$; Cerebral vol: $t = -0.62$; $p = 0.54$	$F_{1,88} = 1.20$; $p = 0.28$	9.37 (7.64)	4.28 (2.79)	$T = -3.53$; $p = 0.001$	12.91 (15.10)	2.51 (5.35)	Group: $t = -4.95$; $p < 0.0001$; Cerebral vol: $t = 2.31$; $p = 0.02$	$F_{1,85} = 5.75$; $p < 0.02$
8.32 (2.55)	Group: $t = 2.95$; $p = 0.004$; Cerebral vol: $t = 1.13$; $p = 0.26$	$F_{1,88} = 4.05$; $p < 0.05$	7.31 (1.21)	7.64 (0.96)	$T = 1.38$; $p = 0.17$	7.14 (2.38)	7.72 (1.87)	Group: $t = 1.13$; $p = 0.26$; Cerebral vol: $t = 2.36$; $p = 0.02$	$F_{1,85} = 0.30$; $p = 0.59$
1.70 (0.77)	Group: $t = 1.80$; $p < 0.08$; Cerebral vol: $t = 1.56$; $p = 0.12$	$F_{1,88} = 5.28$; $p < 0.03$	1.55 (0.34)	1.50 (0.33)	$T = -0.69$; $p = 0.49$	1.60 (0.66)	1.48 (0.64)	Group: $t = -0.98$; $p = 0.33$; Cerebral vol: $t = 2.36$; $p = 0.02$	$F_{1,85} = 0.003$; $p = 0.96$
0.75 (0.34)	Group: $t = 0.89$; $p = 0.38$; Cerebral vol: $t = 1.08$; $p = 0.28$	$F_{1,88} = 0.43$; $p = 0.52$	0.67 (0.13)	0.73 (0.14)	$T = 1.95$; $p = 0.05$	0.64 (0.27)	0.75 (0.27)	Group: $t = 1.89$; $p = 0.06$; Cerebral vol: $t = 0.23$; $p = 0.82$	$F_{1,85} = 0.15$, $p = 0.70$
0.63 (0.31)	Group: $t = 1.10$; $p = 0.27$; Cerebral vol: $t = 1.06$, $p = 0.29$	$F_{1,88} = 0.76$; $p = 0.38$	0.59 (0.17)	0.60 (0.11)	$T = 0.64$; $p = 0.53$	0.57 (0.33)	0.61 (0.23)	Group: $t = 0.56$; $p = 0.58$; Cerebral vol: $t = 0.61$; $p = 0.54$	$F_{1,85} = 3.02$; $p < 0.09$
0.93 (0.35)	Group: $t = 2.54$; $p < 0.02$; Cerebral vol: $t = 0.90$; $p = 0.37$	$F_{1,88} = 2.12$; $p = 0.15$	0.82 (0.15)	0.87 (0.14)	$T = 1.48$; $p = 0.14$	0.79 (0.30)	0.88 (0.28)	Group: $t = 1.25$; $p = 0.21$; Cerebral vol: $t = 2.18$; $p = 0.03$	$F_{1,85} = 0.78$; $p = 0.38$
0.82 (0.33)	Group: $t = 2.60$; $p = 0.01$; Cerebral vol: $t = 0.17$; $p = 0.68$	$F_{1,88} = 2.79$; $p < 0.1$	0.74 (0.17)	0.80 (0.12)	$T = 1.96$; $p = 0.05$	0.70 (0.33)	0.81 (0.24)	Group: $t = 1.74$; $p < 0.09$; Cerebral vol: $t = 2.21$; $p < 0.03$	$F_{1,85} = 0.24$; $p = 0.63$
0.76 (0.32)	Group: $t = 3.98$; $p < 0.0001$; Cerebral vol: $t = -0.58$; $p = 0.56$	$F_{1,88} = 0.11$; $p = 0.74$	0.65 (0.16)	0.67 (0.15)	$T = 0.73$; $p = 0.47$	0.64 (0.32)	0.68 (0.29)	Group: $t = 0.62$; $p = 0.53$; Cerebral vol: $t = 0.90$; $p = 0.37$	$F_{1,85} = 0.005$; $p = 0.95$
2.37 (0.75)	Group: $t = 2.95$; $p < 0.004$; Cerebral vol: $t = 1.16$; $p = 0.25$	$F_{1,88} = 4.27$; $p = 0.05$	2.00 (0.36)	2.17 (0.32)	$T = 2.25$; $p = 0.03$	1.91 (0.70)	2.22 (0.63)	Group: $t = 2.01$; $p = 0.05$; Cerebral vol: $t = 2.50$; $p < 0.02$	$F_{1,85} = 0.42$; $p = 0.52$

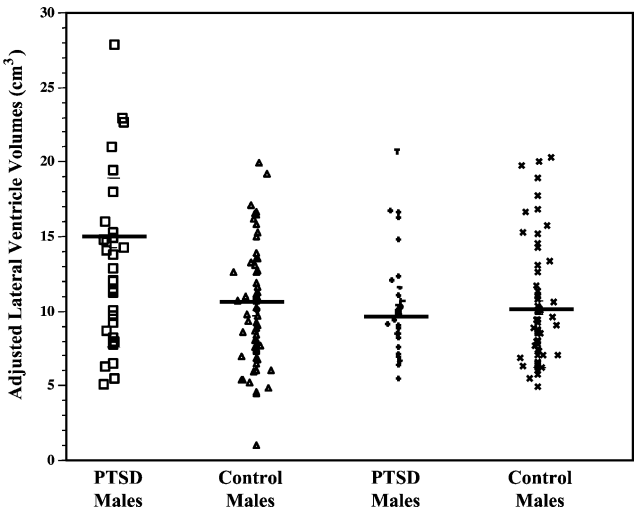

Fig. 1. Total lateral ventricle volumes adjusted for intracranial volume means (cm^3) of maltreated male and female children and adolescents with PTSD and non-maltreated male and female healthy controls (□: PTSD males, $n = 31$; △: control males $n = 62$; +: PTSD females, $n = 30$; ×: control females, $n = 60$).

$r_{28} = 0.28$, $p = 0.13$) subjects with PTSD. On the other hand, significant age*group interactions revealed that maltreated female subjects with PTSD showed greater age related increases in prefrontal CSF volume compared to non-maltreated female controls. However, both comparison female ($rs_{58} = 0.63$, $p < 0.0001$) and maltreated female ($rs_{28} = 0.47$, $p < 0.01$) subjects showed significant increases in prefrontal CSF with age. Comparison male ($r_{60} = 0.15$, $p = 0.26$) and maltreated male ($r_{29} = 0.20$, $p = 0.28$) subjects did not showed significant increases in prefrontal CSF with age. These above significant age by diagnostic group interactions persisted in separate analyses excluding those subjects with PTSD and co-morbid ADHD.

In the overall sample, significant age-related decreases in cerebral grey matter and increases in cerebral white matter volumes and corpus callosum areas were evident in the overall sample, while intracranial and cerebral volumes did not change significantly in this age group. These findings were previously reported or replicated findings of other investigators [35,37,59,60].

3.4. Relationship between brain structures, sex, and clinical factors

Brain structures of PTSD subjects were adjusted for cerebral volume and correlated separately with clinical data using Spearman correlations. As previously reported, intracranial and cerebral volumes each correlated negatively with the duration of the maltreatment experience (in years) that led to the PTSD diagnosis ($rs_{59} = -0.33$, $p = 0.009$; $rs_{59} = -0.33$, $p = 0.01$). As previously reported, intracranial and cerebral volumes each correlated positively with

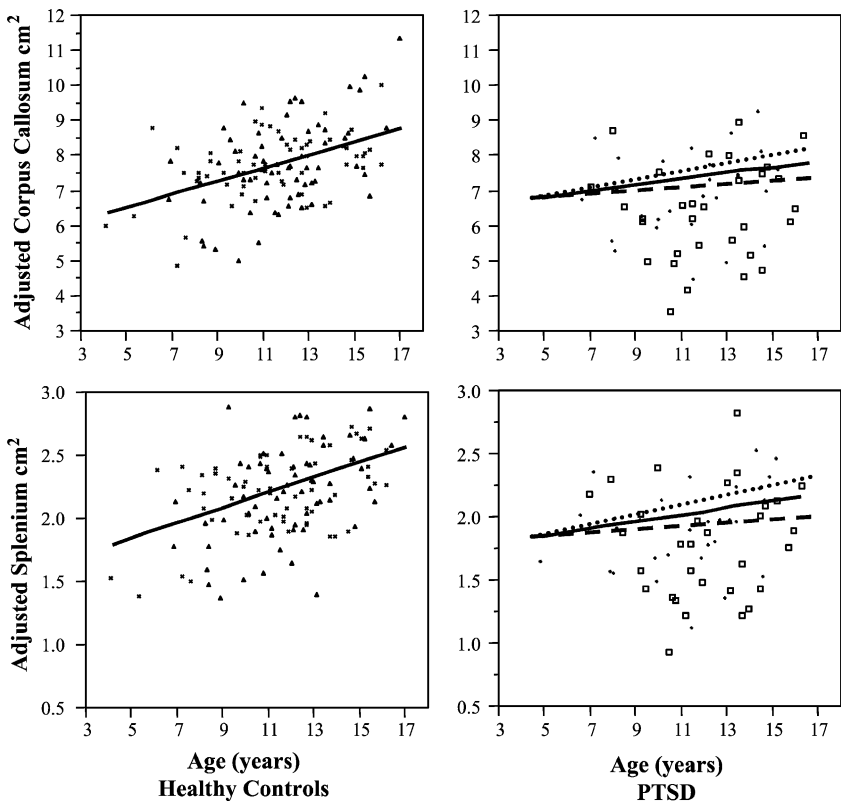

Fig. 2. Relationships between adjusted total corpus callosum and its region 7 (splenium) with age in non-maltreated male and female healthy controls and maltreated male and female children and adolescents with PTSD (□: PTSD males, $n = 31$; △: control males, $n = 62$; +: PTSD females, $n = 30$; ×: control females, $n = 60$; ••••: *PTSDfemales*;n = 60;▬ ▬: *PTSDmales*).

age of onset of maltreatment ($rs_{59} = 0.42$, $p = 0.0008$; $rs_{59} = 0.38$, $p = 0.002$). As previously reported, total corpus callosum area and its posterior subregions correlated negatively with cluster PTSD B, C, and D symptoms, symptoms of childhood dissociation, and CBCL internalizing T score. Lateral ventricle volumes correlated positively with cluster PTSD symptoms, CBCL externalizing T score, and total CBCL T score ($p < 0.05$).

Intracranial and cerebral volumes correlated or showed a trend to correlate negatively with the duration of the maltreatment experience (in years) that led to a PTSD diagnosis ($rs_{28} = -0.44$, $p = 0.01$; $rs_{28} = -0.47$, $p = 0.009$) and positively with age of onset of maltreatment ($rs_{28} = 0.34$, $p = 0.06$; $rs_{28} = 0.32$, $p = 0.08$) when separate analyses were undertaken in females with PTSD. However, the findings were not as clear for males with PTSD regarding intracranial and cerebral volumes and duration ($rs_{29} = -0.18$, $p = 0.32$; $rs_{29} = -0.20$, $p = 0.28$), but PTSD males did show findings suggestive of positive correlations with age of onset of PTSD ($rs_{29} = 0.31$, $p = 0.09$; $rs_{29} = 0.28$, $p = 0.12$). Additionally, prefrontal lobe CSF also correlated positively with age of onset of maltreatment in males ($rs_{29} = 0.45$, $p = 0.01$), but not in females with PTSD. All other significant correlations did not persist when separate analyses were undertaken in gender groups.

4. Discussion

In this study, brain structural differences were examined between maltreated children and adolescents with PTSD and non-maltreated comparison subjects within each gender group to examine sex differences in brain maturation that may be related to having a history of chronic and severe stress. As previously reported, our overall between group findings of smaller intracranial and cerebral volumes and total midsagittal area of corpus callosum, and its posterior subregions and larger total lateral ventricle and prefrontal CSF volumes in PTSD subjects compared with comparison subjects were seen. However, the ability to examine a relatively large sample of male and female pediatric patients with PTSD and healthy comparison subjects revealed a more complex developmental picture. Sex by group effects suggested that there were sex differences in the brain maturation of boys and girls with maltreatment-related PTSD, who suffered from similar traumas and had similar histories of co-morbid mental illness, behavioral problems and cognitive deficits. To our knowledge, this is the first study to comprehensively report gender and age specific changes in brain maturation in a relatively large and gender matched sample of psychotropic-naïve maltreated children and adolescents with chronic PTSD and healthy non-maltreated controls.

Findings of larger prefrontal lobe CSF volumes and smaller midsagittal area of the corpus callosum subregions 7 (splenium) were common to both boys and girls with maltreatment-related PTSD compared to their gender-matched comparison subjects. Larger prefrontal CSF volumes may indicate delayed maturation of the prefrontal cortex. Maturation of the medial prefrontal cortex parallels the acquisition of inhibitory control of amygdala and related nuclei and circuitry [61], structures responsible for fear and anxiety behaviors, and basal ganglion structures, structures involved in impulse control [62]. Maltreated male and female children and adolescents with PTSD had lower *N*-acetylaspartate/creatine ratios, that were suggestive of neuronal loss in the anterior cingulate region of the medial prefrontal cortex, compared to sociodemographically and IQ matched controls [63]. Positron emission tomography (PET) investigations provide evidence for medial prefrontal cortex dysfunction in adult PTSD [64–66].

Maltreated male and female children with PTSD did not show the normal age related increases in the area of the total corpus callosum and its region 7 (splenium) compared to non-maltreated controls. This finding was more prominent in traumatized males. Sex differences were also reported in the subregions of the corpus callosum in physically abused and neglected children who were not evaluated for PTSD compared to psychiatrically ill non-maltreated controls [67]. Similarly, nursery-reared male rhesus monkeys 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 [68]. The results from this study are also similar to the previous literature on the effects of early experience on the development of the corpus callosum in rodents [69,70]. These studies also showed that the effects of early experience on myelination and corpus callosum axonal diameter is modulated by gender. While rats of both sexes had a larger posterior third of the corpus callosum if they were raised in the complex environment, plasticity in the females occurred through changes in myelination and axon number [70] and in males, through increasing axon size [69,70].

Predominantly posterior increases in corpus callosum size are seen during normal childhood development in cross-sectional [60] and longitudinal studies [35]. This increase is thought to reflect the development of interhemispheric connections among association regions and to be influenced by environmental stimulation and adversity. Maltreated children suffer from a variety of co-occurring developmental consequences including adverse emotional [5–7], behavioral [5], and cognitive consequences [8]. A possible neurobiological mechanism for these global adverse outcomes may be related to this lack of age-related corpus callosal growth.

Despite similar ages of onset, duration, length of time since disclosure, and similar types of abuse between the male and female pediatric PTSD patients, the results of this study provided evidence that maltreated males with PTSD

show more evidence of adverse brain development than maltreated females with PTSD. Male children utilize psychiatric services at higher rates and are at greater risk than female children for developmental neuropsychiatric disorders [71]. Men and women differ in the rate and course of specific psychopathological syndromes [72]. Cross-sectional investigations of human aging have suggested that there may be greater age-related atrophy in males compared to females [73–78]. Furthermore, females demonstrate less susceptibility to postischemic and post-traumatic brain injury than males in experimental animal models and clinical cases [79]. These findings may be mediated by the gonadal hormones, since estradiol positively influences hippocampal cell proliferation, number of dendritic spines and synaptogenesis [80–82], delays in synaptic pruning in other brain regions [83] and has an antioxidant effect as well as an neurotoxicity reduction effect [79]. Thus being male may constitute a neurobiologic risk marker for stress-related vulnerability for adverse brain development during childhood. This risk marker may have a 'sleeper effect.' Interestingly, 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 (<age 11 years) child abuse and/or neglect, compared with sociodemographically matched controls, maltreated males demonstrated lower levels of a comprehensive measure of resilience as adults than maltreated females [84].

Maltreated males with PTSD did show a trend towards toward reporting of more PTSD cluster C symptoms than maltreated females with PTSD. Cluster C symptoms represent both avoidant and dissociative behaviors and can be thought of as ways to control painful and distressing re-experiencing of symptoms. These include efforts to avoid traumatic reminders, diminished interest in others, feelings of detachment, a restricted range of affect, and dissociation. However, emotional numbing and diminished interest in others, particularly during development, may result in lack of empathy and an increased risk for antisocial behaviors, as well as PTSD symptoms and externalizing behaviors. Maltreated males with PTSD also demonstrated findings suggestive of a smaller region 1 (rostrum) of the corpus callosum as well as a lack of age-appropriate myelination of this structure with age. The rostrum is a region which serves the axons of the prefrontal and orbital frontal cortex, and is involved in attachment and inhibitory behaviors [85,86]. The greater male vulnerability for adverse neurobiologic consequences associated with the experience of severe maltreatment-related stress during development may make males more vulnerable to antisocial behaviors [14]. A study [87] reported that in a sample of male incarcerated juvenile offenders, 32% fulfilled and another 20% met partial criteria for PTSD, most commonly from intrafamilial abuse. There is a sociobiological basis for these speculative ideas [88]. Emotional numbing and detachment behaviors during adverse circumstances (i.e. killing game, warfare) would be more beneficial to male than to female primitive human gene survival. This tendency for males to show evidence for more adverse brain development than females while showing similar levels of childhood psychopathology may be a marker for future antisocial behavior. Interestingly, follow-up of males subjects from the original study [40] revealed that eight of 25 males and only one of the 19 females with PTSD studied and none of the controls developed conduct disorder or were arrested on more than one occasion within 3 years of initial brain scan.

Unlike studies in adult PTSD where specific changes were seen in the hippocampus, pediatric maltreatment-related PTSD is associated with evidence of loss of prefrontal cortex integrity [63], deficits in myelination of posterior brain regions and larger superior temporal gyrus volumes [89], that were not related to gender. However, findings of global adverse brain maturation were more prominent in male subjects with PTSD. Furthermore, the nature of the brain maturation findings in traumatized males and females may indicate that males are more likely to suffer neurotoxity given the same degree of psychological insult and behavioral symptoms. Males were more likely to have significant age of onset effects for cerebral volume and prefrontal CSF volumes. Females were more likely to have cumulative effects of trauma (duration of trauma effects) as well as age of onset effects for these brain regions. These findings differ from studies of non-traumatized children and adolescents with generalized anxiety disorder, which was associated with larger and particularly right sided amygdala [44] and the superior temporal gyrus [45] volumes. Consequently, maltreatment-related PTSD may be regarded as a complex environmentally induced developmental disorder.

This cross-sectional investigation does not imply causation. The results of this pediatric imaging study is limited because we only studied childhood trauma in those subjects who develop PTSD. Thus we can not disentangle whether our observed sex difference are a consequence of the stress and trauma or a preexisting risk factor for the development of PTSD. One should note the recent study by Gilbertson et al., which suggested that reduced hippocampal size is not a consequence of trauma exposure and PTSD, but instead may be a risk factor for the development of PTSD [90]. However, it is unlikely that the sex differences reported here are primarily related to having a pediatric anxiety disorder. These structural and age-related neurobiological brain maturation sex differences may help the childhood traumatic stress field identify mechanisms for adverse brain development and compromised psychosocial outcomes that are commonly seen in victims of childhood maltreatment. Because sex differences are relatively small compared to the known developmental variability in volume of brain structures, developmental MRI brain studies need to be of sufficient power to comprehensively examine sex differences. Future MRI brain investigations of childhood PTSD and the longitudinal relationship of these findings to PTSD

symptoms, gender and psychosocial outcomes are warranted.

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References

[1] Widom CS. Posttraumatic stress disorder in abused and neglected children grown up. Am J Psychiatry 1999;156:1223–9.
[2] Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes if death in adults. Am J Prevent Med 1998;14:245–58.
[3] Pynoos RS, Steinberg AM, Wraith R. A developmental model of childhood traumatic stress. In: Cicchetti D, Cohen DJ, editors. Developmental psychopathology. New York: Wiley; 1995. p. 72–95.
[4] De Bellis MD. Posttraumatic stress disorder and acute stress disorder. In: Ammerman RT, Hersen M, editors. Handbook of prevention and treatment with children and adolescents. New York: Wiley; 1997. p. 455–94.
[5] Shields AM, Cicchetti D, Ryan R. The development of emotional and behavioral self-regulation and social competence among maltreated school-age children. Dev Psychopathol 1994;6:57–75.
[6] National Research Council, Understanding child abuse and neglect. Washington, DC: National Academy Press; 1993.
[7] Cicchetti D, Lynch M. Failures in the expectable environment and their impact on individual development: the case of child maltreatment. In: Cicchetti D, Cohen DJ, editors. Developmental psychopathology. New York: Wiley; 1995. p. 32–71.
[8] Cahill LT, Kaminer RK, Johnson PG. Developmental cognitive and behavioral sequelae of child abuse. Child Adolesc Psychiatr Clin N Am 1999;8:827–43.
[9] Famularo R, Fenton T, Augustyn M, Zuckerman B. Persistence of pediatric post traumatic stress disorder after 2 years. Child Abuse Neglect 1996;20:1245–8.
[10] McLeer SV, Dixon JF, Henry D, Ruggiero K, Escovitz K, Niedda T, Scholle R. Psychopathology in non-clinically referred sexually abused children. J Am Acad Child Adolesc Psychiatry 1998;37:1326–33.
[11] Kessler RC. Posttraumatic stress disorder: the burden to the individual and to society. J Clin Psychiatry, 61 2000;61(Suppl 5):4–12.
[12] American Psychiatric Association, Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Press; 2000. Text revision, p. 424–32.
[13] Fletcher KE. Childhood posttraumatic stress disorder. In: Mash EJ, Barkley RA, editors. Child psychopathology. New York: Guilford Publications; 1996. p. 242–76.
[14] De Bellis MD. Developmental traumatology: tshe psychobiological development of maltreated children and its implications for research, treatment, and policy. Dev Psychopathol 2001;13:537–61.
[15] Carrion VG, Weems CF, Ray RD, Reiss AL. Toward an empirical definition of pediatric PTSD: the phenomenology of PTSD symptoms in youth. J Am Acad Child Adolesc Psychiatry 2001;41:166–73.
[16] De Bellis MD, Broussard E, Wexler S, Herring D, Moritz G. Psychiatric co-morbidity in caregivers and children involved in maltreatment: a pilot research study with policy implications. Child Abuse Neglect 2001;25:923–44.
[17] Kendler KS, Bulik CM, Silberg J, Hettema JM, Myers J, Prescott CA. Childhood sexual abuse and adult psychiatric and substance use disorders in women: an epidemiological and cotwin control study. Arch Gen Psychiatry 2000;57:953–9.
[18] Edwards E, Harkins K, Wright G, Menn F. Effects of bilateral adrenalectomy on the induction of learned helplessness. Behav Neuropsychopharmacol 1990;3:109–14.
[19] Sapolsky RM, Uno H, Rebert CS, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J Neurosci 1990;10:2897–902.
[20] Simantov R, Blinder E, Ratovitski T, Tauber M, Gabbay M, Porat S. Dopamine induced apoptosis in human neuronal cells: inhibition by nucleic acids antisense to the dopamine transporter. Neuroscience 1996;74:39–50.
[21] Smythies JR. Oxidative reactions and schizophrenia: a review–discussion. Schizophrenia Res 1997;24:357–64.
[22] Dunlop SA, Archer MA, Quinlivan JA, Beazley LD, Newnham JP. Repeated prenatal corticosteroids delay myelination in the ovine central nervous system. J Maternal–Fetal Med 1997;6:309–13.
[23] Lauder JM. Neurotransmitters as morphogens. Prog Brain Res 1988;73:365–88.
[24] Todd RD. Neural development is regulated by classical neurotransmitters: dopamine D2 receptor stimulation enhances neurite outgrowth. Biol Psychiatry 1992;31:794–807.
[25] Tanapat P, Galea LA, Gould E. Stress inhibits the proliferation of granule cell precursors in the developing dentate gyrus. J Dev Neurosci 1998;16:235–9.
[26] Gould E, Tanapat P, Cameron HA. Adrenal steroids suppress granule cell death in the developing dentate gyrus through an NMDA receptor-dependent mechanism. Brain Res Dev Brain Res 1997;103:91–3.
[27] Gould E, Tanapat P, McEwen BS, Flugge G, Fuchs E. Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc Natl Acad Sci USA 1998;95:3168–71.
[28] Smith MA, Makino S, Kvetnansky R, Post RM. Effects of stress on neurotrophic factor expression in the rat brain. Ann NY Acad Sci 1995;771:234–9.
[29] Huttenlocher PR. Synaptic density in human frontal cortex-developmental changes and effects of aging. Brain Res 1979;163:195–205.
[30] Yakovlev PI, LeCours AR. The myelogenetic cycles of regional maturation of the brain. In: Minkowski A, editor. Regional development of the brain in early life. Philadelphia, PA: Davis; 1967. p. 3–70.
[31] Jernigan TL, Sowell ER. Magnetic resonance imaging studies of the developing brain. In: Keshavan MS, Murray RM, editors. Neurodevelopment and adult psychopathology. United Kingdom: Cambridge University; 1997. p. 63–70.
[32] Giedd JN, Blumenthal J, Jeffries NO, Castellanos X, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. Brain development during

childhood and adolescence: a longitudinal MRI study. Nat Neurosci 1999;2:861–3.
[33] Thompson PM, Giedd JN, Woods RP, MacDonald D, Evans AC, Toga AW. Growth patterns in the developing brain detected by using continuum mechanical tensor maps. Nature 2000;404:190–3.
[34] Giedd JN, Castellanos FX, Casey BJ, Kozuch BA, King AC, Hamburger SD, Rapoport JL. Quantitative morphology of the corpus callosum in attention deficit hyperactivity disorder. Am J Psychiatry 1994;151:665–9.
[35] Giedd JN, Blumenthal J, Jeffries NO, Rajapakse JC, Vaituzis AC, Liu H, Tobin M, Nelson J, Castellanos X. Development of the human corpus callosum during childhood and adolescence: a longitudinal MRI study. Prog NeuroPsychopharmacol Biol Psychiatry 1999;23: 571–88.
[36] McEwen BS. Neural gonadal steroid actions. Science 1981;211: 1303–11.
[37] De Bellis MD, Keshavan MS, Beers SR, Hall J, Frustaci K, Masalehdan A, Noll J, Boring AM. Sex differences in brain maturation during childhood and adolescence. Cerebral Cortex 2001;11:552–7.
[38] Gur RC, Turetsky BI, Matsui M, Yan M, Bilker W, Hughett P, Gur RE. Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. J Neurosci 1999;19: 4065–72.
[39] Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925–35.
[40] De Bellis MD, Keshavan M, Clark DB, Casey BJ, Giedd J, Boring AM, Frustaci K, Ryan ND. A.E. Bennett research award. Developmental traumatology part II: brain development. Biol Psychiatry 1999;45:1271–84.
[41] De Bellis MD, Keshavan M, Shifflett H, Iyengar S, Beers SR, Hall J, Moritz G. Brain structures in pediatric maltreatment-related PTSD: a sociodemographically matched study. Biol Psychiatry 2002; 52: 1066–1078.
[42] Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, Reiss AL. Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. Biol Psychiatry 2001;50:943–51.
[43] De Bellis MD, Hall J, Boring AM, Frustaci K, Moritz G. A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. Biol Psychiatry 2001;50:305–9.
[44] De Bellis MD, Casey BJ, Dahl R, Birmaher B, Williamson D, Thomas KM, Axelson DA, Frustaci K, Boring AM, Hall J, Ryan N. A pilot study of amygdala volumes in pediatric generalized anxiety disorder. Biol Psychiatry 2000;48:51–7.
[45] De Bellis MD, Keshavan M, Shifflett H, Iyengar S, Dahl R, Axelson DA, Birmaher B, Hall J, Moritz G, Ryan N. Superior temporal gyrus volumes in pediatric generalized anxiety disorder. Biol Psychiatry 2002;51:553–62.
[46] Overman WH, Bachevalier J, Schuhmann E, McDonough-Ryan P. Sexualy dimorphic brain-behavior development: a comparative perspective. In: Krasnegor NA, Lyon GR, Goldman-Rakic PS, editors. Development of the prefrontal cortex. Baltimore, MD: Paul H Brookes Publishing Co Inc; 1997. p. 337–58.
[47] Nagy Jacklin C, Martin LJ. Effects of gender on behavior and development. In: Levine MD, Carey WB, Crocker AC, editors. Developmental–behavioral pediatrics, 3rd ed. Philadelphia: W.B. Saunders; 1999. p. 100–6.
[48] Lange N, Giedd JN, Castellanos FX, Vaituzis AC, Rapoport JL. Variability of human brain structure size: ages 4–20 years. Psychiatry Res: Neuroimaging Sec 1997;74:1–12.
[49] Perez C, Widom CS. Childhood victimization and long-term intellectual and academic outcomes. Child Abuse Neglect 1994; 18(8):617–33.
[50] Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. 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 1997;36(7):980–8.
[51] Scheeringa MS, Zeanah CH, Drell MJ, Larrieu JA. Two approaches to the diagnosis of posttraumatic stress disorder in infancy and early childhood. J Am Acad Child Adolesc Psychiatry 1995;34:191–200.
[52] Kovacs M. The children's depression inventory (CDI). Psychopharmacol Bull 1985;21:995–8.
[53] Achenbach TM, Edelbrock CS. Manual for the child behavior checklist. Department of Psychiatry, University of Vermont, Burlington, VT: Queen City Printers; 1983.
[54] Putnam FW, Peterson G, Eds. Further validation of the child dissociative checklist, Dissociation, VII; 1994. p. 204–11
[55] Rasband W. NIH IMAGE manual. Bethesda, MD: National Institutes of Health; 1996.
[56] Keshavan MS, Anderson S, Beckwith C, Nash K, Pettegrew JW, Krishman RR. A comparison of stereology and segmentation techniques for volumetric measurements of lateral ventricles in magnetic resonance imaging. Psychiatr Res: Neuroimaging 1995;61: 53–60.
[57] Keshavan MS, Beckwith C, Bagwell W, Pettegrew JW, Krishman RR. An objective method for edge detection in MRI morphometry. Eur J Psychiatry 1994;9:205–7.
[58] Rosenberg DR, Keshavan MS, O'Hearn KM, Dick EL, Bagwell WW, Seymour AB, Montrose DM, Pierri JN, Birmaher B. Frontostriatal measurement in treatment-naive children with obsessive-compulsive disorder. Arch Gen Psychiatry 1997;54:824–30.
[59] Giedd JN, Snell JW, Lange N, Rajapakse JC, Kaysen D, Vaituzis AC, Vauss YC, Hamburger SD, Kouch PL, Rapoport JL. Quantitative magnetic resonance imaging of human brain development: ages 4–18. Cerebral Cortex 1996;6:551–60.
[60] Giedd JN, Rumsey JM, Castellanos FX, Rajapakse JC, Kaysen D, Vaituzis AC, Vauss YC, Hamburger SD, Rapoport JL. A quantitative MRI study of the corpus callosum in children and adolescents. Dev Brain Res 1996;91:274–80.
[61] LeDoux J. Fear and the brain: where have we been, and where are we going? Biol Psychiatry 1998;44:1229–38.
[62] Swanson J, Castellanos FX, Murias M, LaHoste G, Kennedy J. Cognitive neuroscience of attention deficit hyperactivity disorder and hyperkinetic disorder. Curr Opin Neurobiol 1998;8:263–71.
[63] De Bellis MD, Keshavan MS, Spencer S, Hall J. *N*-acetylaspartate concentration in the anterior cingulate in maltreated children and adolescents with PTSD. Am J Psychiatry 2000;157:1175–7.
[64] Shin LM, McNally RJ, Kosslyn SM, Thompson WL, Rauch SL, Alpert NM, Metzger LJ, Lasko NB, Orr SP, Pitman RK. Regional cerebral blood flow during script-imagery in childhood sexual abuse-related PTSD: a PET investigation. Am J Psychiatry 1999;156: 575–84.
[65] Bremner JD, Narayan M, Staib L, Southwick SM, McGlashan T, Charney DS. Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. Am J Psychiatry 1999;156:1787–95.
[66] Bremner JD, Staib L, Kaloupek D, Southwick SM, Soufer R, Charney DS. Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. Biol Psychiatry 1999;45:806–16.
[67] Teicher MH, Ito Y, Glod CA, Andersen SL, Dumont N, Ackerman E. Preliminary evidence for abnormal cortical development in physically and sexually abused children using EEG coherence and MRI. Yehuda R, McFarlane C, editors. Ann NY Acad Sci 1997; 160–75.
[68] Sanchez MM, Hearn EF, Do D, Rilling JK, Herndon JG. Differential rearing affects corpus callosum size and cognitive function of rhesus monkeys. Brain Res 1998;812:38–49.
[69] Berrebi AS, Fitch RH, Ralphe DL, Denenberg JO, Friedrich VLJ, Denenberg VH. Corpus callosum: region-specific effects of sex, early experience and age. Brain Res 1988;438:216–24.

[70] Juraska JM, Kopcik JR. Sex and environmental influences on the size and ultrastructure of the rat corpus callosum. Brain Res 1988;450: 1–8.
[71] Earls F. Sex differences in psychiatric disorders: origins and developmental influences. Psychiatr Dev 1987;1:1–23.
[72] Seeman MV. Psychopathology in women and men: focus on female hormones. Am J Psychiatry 1997;154.
[73] Coffey CE, Lucke JF, Saxton JA, Ratcliff G, Billig B, Bryan RN. Sex differences in brain aging: a quantitative magnetic resonance imaging study. Arch Neurol 1998;55:169–79.
[74] Cowell PE, Turetsky BI, Gur RC, Grossman RI, Shtasel DL, Gur RE. Sex differences in aging of the human frontal and temporal lobes. J Neurosci 1994;14:4748–55.
[75] Gur RC, Mozley PD, Resnick SM, Gottlieb G, Kohn M, Zimmerman RA, Herman G, Atlas S, Grossman R, Berretta DA, Erwin R, Gur RE. Gender differences in age effect on brain atrophy measured by magnetic resonance imaging. Proc Natl Acad Sci 1991;88: 2845–9.
[76] Kaye JA, DeCarli C, Luxenberg JS, Rapoport SI. The significance of age-related enlargement of the cerebral ventricles in healthy men and women measured by quantitative computed X-ray tomography. Am J Geriatr Soc 1992;40:225–31.
[77] Murphy DGM, DeCarli C, McIntosh AR, Daly E, Mentis MJ, Pietrini P, Szczepanik J, Schapiro MB, Grady CL, Horwitz B, Rapoport SI. Sex differences in human brain morphometry and metabolism: an in vivo quantitative magnetic resonance imaging and positron emission tomography study on the effects of aging. Arch Gen Psychiatry 1996; 53:585–94.
[78] Xu J, Kobayashi S, Yamaguchi S, Iijima K, Okada K, Yamashita K. Gender effects on age-related changes in brain structure. AJNR: Am J Neuroradiol 2000;21:112–8.
[79] Roof RL, Hall ED. Gender differences in acute CNS trauma and stroke: neuroprotective effects of estrogen and progesterone. J Neurotrauma 2000;17:367–88.
[80] Gould E, Woolley CS, Frankfurt M, McEwen BS. Gonadal steroids regulate dendritic spine density in hippocampal cells in adulthood. J Neurosci 1990;10:1286–91.
[81] Tanapat P, Hastings NB, Reeves AJ, Gould E. Estrogen stimulates a transient increase in the number of new neurons in the dentate gyrus of the adult female rat. J Neurosci 1999;19:5792–801.
[82] Woolley CS, Jurgen Wenzel H, Schwartzkroin PA. Estradiol increases the frequency of multiple synapse boutons in the hippocampal CA1 region pf the adult female rat. J Compar Neurol 1996;373:108–17.
[83] Naftolin F, Garcia-Segura LM, Keefe D, Leranth C, Maclusky NJ, Brawer JR. Estrogen effects on the synaptology and neural membranes of the rat hypothalamic arcuate nucleus. Biol Reprod 1990;42:21–8.
[84] McGloin JM, Widom CS. Resilience among abused and neglected children grown up. Dev Psychopathol 2001;13:1021–38.
[85] Lorberbaum JP, Newman JD, Dubno JR, Horwitz AR, Nahas Z, Teneback CC, Bloomer CW, Bohning DE, Vincent D, Johnson MR, Emmanuel N, Brawman-Mintzer O, Book SW, Lydiard RB, Ballenger JC, George MS. Feasibility of using fMRI to study mothers responding to infant cries. Depression Anxiety 1999;10:99–104.
[86] Schore AN. Attachment and the regulation of the right brain. Attach Hum Dev 2000;2:23–47.
[87] Steiner H, Garcia IG, Matthews Z. Posttraumatic stress disorder in incarcerated juvenile delinquents. J Am Acad Child Adolesc Psychiatry 1997;36:357–65.
[88] Wilson EO. On human nature. Cambridge: Harvard University Press; 1978.
[89] De Bellis MD, Keshavan M, Frustaci K, Shifflett H, Iyengar S, Beers SR, Hall J. Superior temporal gyrus volumes in maltreated children and adolescents with PTSD. Biol Psychiatry 2002;51:544–52.
[90] Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 2002;5:1242–7.