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# Converging evidence for abnormalities of the prefrontal cortex and evaluation of midsagittal structures in pediatric PTSD: an MRI study

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## Abstract

**Objective**—Volumetric imaging research has shown abnormal brain morphology in posttraumatic stress disorder (PTSD) when compared to controls. We present results on a study of brain morphology in the prefrontal cortex (PFC) and midline structures, via indices of gray matter volume and density, in pediatric PTSD. We hypothesized that both methods would demonstrate aberrant morphology in the PFC. Further, we hypothesized aberrant brainstem anatomy and reduced corpus collosum volume in children with PTSD.

**Methods**—Twenty-four children (aged 7-14) with history of interpersonal trauma and 24 age, and gender matched controls underwent structural magnetic resonance imaging. Images of the PFC and midline brain structures were first analyzed using volumetric image analysis. The PFC data were then compared with whole-brain voxel-based techniques using statistical parametric mapping (SPM).

**Results**—The PTSD group showed significant increased gray matter volume in the right and left inferior and superior quadrants of the prefrontal cortex and smaller gray matter volume in pons, and posterior vermis areas by volumetric image analysis. The voxel-by-voxel group comparisons demonstrated increased gray matter density mostly localized to ventral PFC as compared to the control group.

**Conclusions**—Abnormal frontal lobe morphology, as revealed by separate-complementary image analysis methods, and reduced pons and posterior vermis areas are associated with pediatric PTSD. Voxel-based morphometry may help to corroborate and further localize data obtained by volume of interest methods in PTSD.

## Keywords

Statistical Parametric Mapping; frontal lobe; child maltreatment; early life stress; pons; vermis

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## 1. INTRODUCTION

Sixty percent of males and 50% percent of females will be exposed to a traumatic event (i.e.; a life threatening event) in their lifetime and about 20% of these individuals will develop posttraumatic stress disorder (PTSD) (Breslau et al 1998, Breslau et al 1999). Prevalence in children may be higher (Ackerman et al 1998, McLeer et al 1998).

The availability of magnetic resonance imaging (MRI) has facilitated the study of brain morphology in PTSD. The last decade has seen extensive brain volumetric research in adult PTSD (Rauch et al 1998). Structural imaging studies have suggested that adult PTSD patients have altered brain morphology when compared to controls (Bremner et al 1995, Bremner et al 1997, Gurvits et al 1997, Stein et al 1997). Studies of brain volumes in adult patients with PTSD have focused in studying limbic areas, such as the hippocampus. Memory deficits in adults with PTSD (Bremner et al 1993), make the hippocampus a logical area of interest. Initial findings from cross-sectional studies proposed a decreased volume in both left and right hippocampi of adult PTSD subjects when compared to controls, suggesting a potential biological marker for this syndrome. A more recent twin study, however, challenges this notion. Gilbertson and colleagues studied monozygotic twins discordant for trauma exposure. They found that those pairs with a member with PTSD had significantly smaller hippocampi than non-PTSD pairs. Further, they found that PTSD severity was negatively correlated with the hippocampal volume of both the PTSD subject and their non-trauma exposed identical twin. Their results suggest that hippocampal volume may be a risk factor for PTSD rather than a marker of the disease (Gilbertson et al 2002).

Other brain regions have been studied in adults with PTSD. When comparing cancer survivors with intrusive recollections to survivors without recollections, Matsuoka and colleagues found significantly decreased amygdala volumes in those with intrusive recollections (Matsuoka et al, 2003). Rauch and colleagues found significantly decreased volumes in pregenual anterior cingulate cortex and subcallosal cortex in women with PTSD when compared to trauma-exposed women without PTSD (Rauch et al 2003). Hence, this study implicates pathology of the frontal cortex in PTSD.

Aberrant anatomy of limbic and frontal brain regions may be associated with alterations in brain function. Functional imaging investigations indicate that adults with PTSD show lower activation of frontal regions involved in cognitive functions, such as Broca's area (left inferior frontal gyrus), when compared to normal controls (Rauch et al 1996). Moreover, increased activation has been found in limbic and paralimbic areas, such as the amygdala, orbitofrontal area and prefrontal cortex; specifically in the ventral anterior cingulate gyrus (Rauch et al 1996, Fischer et al 1996, Shin et al 1997, Shin et al 1999).

Recently the study of brain morphology has been extended to pediatric PTSD (De Bellis et al 1999a, Carrion et al 2001). A small number of existing investigations suggest that abnormal brain morphology also may be associated with PTSD in children. In particular, results of recent studies have suggested global brain volume deficits and alterations in anterior cingulate cortex, corpus callosum, and frontal lobe in affected pediatric populations (De Bellis et al 1999a, Carrion et al 2001). Although smaller hippocampal volumes were noted in these cross-sectional studies, the differences were not statistically significant when controlling for total brain volume. Recently, however, our group reported that when studied longitudinally, PTSD symptoms and cortisol levels at baseline predicted hippocampal reduction in children over an ensuing 12-18 month interval (Carrion et al 2007). This reduction may reflect the putative neurotoxic effects of cortisol or a potential stunted growth in this region in vulnerable children. Other areas of interest have been investigated by De Bellis and colleagues. This group replicated previous findings of smaller intracranial and cerebral volumes, and also found

smaller prefrontal cortex volumes (De Bellis et al 2002a). This group has also reported smaller superior temporal gyrus volumes in maltreated children and adolescents (De Bellis et al 2002b) and reduction in the middle, posterior, and total midsagittal area measurements of the corpus callosum along with enlargement of the lateral ventricles (De Bellis et al 1999a; De Bellis et al 2002a).

Although standard volumetric imaging studies can help to elucidate anatomic differences between individuals with PTSD and controls, greater specificity of the location of these anatomic findings is possible with the use of additional, complementary methodologies. Statistical parametric mapping (SPM) is a voxel-based analytic method that has been extensively used in functional imaging studies (Sakurai et al 2001, Davatzikos et al 2001, Verhoeff et al 2000, Stamatakis et al 1999) including studies addressing psychiatric symptoms such as depression and apathy (Kano et al 1992, Migneco et al 2001). SPM analyses can localize regional activation differences between groups by employing spatial standardization of image volumes, computing comparison statistics and testing significance levels. More recently this methodology has been applied successfully to structural/anatomic image data (Woermann et al 1999), including pediatric populations, where it has been found to have utility in illustrating syndrome specific anatomical differences in samples of children with dyslexia, epilepsy and schizophrenia (Brown et al 2001, Muzik et al 2000, Sowell et al 2000).

Frontal lobe abnormalities in pediatric PTSD are of particular interest from the perspectives of developmental psychiatry and cognitive neuroscience. Our laboratory recently reported an attenuation of frontal lobe asymmetry in children with PTSD symptoms, a finding that appeared to be secondary to preservation of left frontal gray matter (Carrion et al 2001). Consistent with a hypothesis of prefrontal dysfunction, children with PTSD perform poorly on Mazes, a supplement to the WISC-III, (as compared to standardized scores) suggesting difficulties with executive function (Beers et al 2002).

In this investigation we sought to more specifically localize morphological differences associated with pediatric PTSD beyond the cerebral lobe level by investigating prefrontal cortex and midsagittal structures. In addition, we utilized a voxel-based analysis of whole brain gray matter to complement prefrontal cortex volumetric analyses. Voxel-based morphometry is an unbiased approach to a comprehensive assessment of the whole brain. In particular, these two methods (voxel-based and volumetric) were utilized to investigate prefrontal cortex gray matter density (defined as the average concentration of gray matter in each voxel) (See Ashburner and Friston 2000) and volume, respectively.

Previous studies have suggested smaller prefrontal volumes in pediatric PTSD (De Bellis et al 2002a). Our previous study in sMRI, however, found increased left frontal gray matter volume in children with PTSD when compared to controls (Carrion et al 2001). Based on this discrepancy we decided to examine prefrontal volumes, we hypothesized that the prefrontal cortex would demonstrate morphological variation in children with PTSD symptoms when compared to healthy controls. We further hypothesized that voxel-based techniques would help to specify which areas of the prefrontal cortex were most aberrant, such as the orbitofrontal area, the prefrontal region most involved in emotion and affect.

The relationship between corpus callosum growth and stress is of interest because this midline structure connects the two brain hemispheres and it has been theorized that early life stress can affect the functional integration of the left and right hemispheres. Communication between the hemispheres may play a role on the development of hemispheric lateralization and dominance (Teicher et al 2002). Of interest, children with PTSD demonstrate increased mixed laterality, suggesting lack of hemispheric differentiation, when compared to controls (Saltzman et al 2006). In here, we theorized that a lack of hemispheric differentiation may result from an

underdeveloped corpus callosum. The link between stress and decreased corpus callosum size has been shown in animal studies. Primate studies have shown that monkeys raised in isolation have decreased corpus callosum size (Sanchez et al 2000). Based on previous work by De Bellis and colleagues (De Bellis et al 1999a; De Bellis et al 2002a) and the potential vulnerability of this structure to stress, we hypothesized reduced corpus callosum areas in children with PTSD.

Brainstem measurements were included in the analysis to underscore the fact that this area houses circuitry relevant to physiological hyperarousal (which are presumed to result from an exaggerated activity of the sympathetic system, and more specifically the locus coeruleus). Brainstem structures are involved in the noradrenergic and adrenaline fight-or-flight response to stress (Teicher et al 2002). The locus coeruleus is a small structure that may not affect the volume of the brainstem overall, however, since physiological hyperarousal is an integral component of the behavioral description of PTSD, we hypothesize volumetric differences between PTSD and controls in this region.

Finally, we also included the cerebellar vermis as an exploratory region of interest since alterations of vermal morphology have been found to be characteristic of many psychiatric and neurodevelopmental conditions (DeBello et al 1999; Mostofsky et al 1998a; Supprian et al 2000). This structure is of particular interest to PTSD because developmentally it houses the highest density of glucocorticoid receptors (Pavlic and Buresova 1984). This is of concern because our laboratory and others have shown increased cortisol levels in children with PTSD when compared to healthy controls (Carrion et al 2002b, De Bellis et al 1999b) and there are reports of potential cytotoxic effects by glucocorticoids (Sapolsky et al 1990). Because of this potential neurotoxicity by stress, we hypothesize smaller vermis volumes in PTSD when compared to controls.

## 2. METHODS

### 2.1 Subjects

The clinical group was recruited from local departments of social services and mental health clinics. All of the subjects fulfilled the following criteria for study inclusion: 1) At least one episode of exposure to trauma, as defined by DSM-IV criterion A1; “the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others” (American Psychiatric Association 1994). 2) Ages 7 to 14 years old. 3) The trauma episode or episodes for which the individual is referred must have occurred at least 6 months prior to referral. 4) A severity score of 12 or above on the PTSD Reaction Index. A score of 12 is the threshold for a PTSD diagnosis of any severity (Nader et al 1990). Exclusion criteria consisted of a PTSD Reaction Index severity score below 12; history of mental retardation; history of schizophrenia or autism, contraindications for MRI including the presence of any metal or electrical conductive implants or foreign bodies; current history of substance dependence and history of clinically significant head trauma, epilepsy, or other documented neurological disorder.

All children in the PTSD sample were referred to the project due to exposure to traumatic events. All referred children underwent screening with the PTSD Reaction Index, and were excluded if they scored less than 12 (12 = mild PTSD). The final sample consisted of 14 boys and 10 girls for a total sample of 24 children. Twenty-two subjects were right-handed and two were left-handed.

The final PTSD group was comprised of 12 subjects who fulfilled DSM-IV diagnostic criteria for PTSD by the The Clinician Administered PTSD Scale for Children and Adolescents (CAPS-CA, see below) and 12 subjects with sub-threshold symptoms by CAPS-CA. We

included all clinical subjects in one sample based on our previous reported findings demonstrating no functional impairment or volumetric differences between these two groups (Carrion et al 2002a, Carrion et al 2001). This final clinical group is the same as that described in an earlier paper from our laboratory (Carrion et al 2001).

The subjects and imaging data comprising the control group were obtained from an archived sample of typically developing controls recruited at the Stanford Psychiatry Neuroimaging Laboratory. Twenty-four right-handed healthy control subjects who had scans with identical acquisition parameters and a documented IQ score were individually age (within 1.5 years) and gender matched to PTSD subjects.

## 2.2 Clinical Evaluation

All subjects and their legal guardians were presented with an IRB approved informed consent and agreed to participate. An in-depth clinical evaluation was conducted on all referred children who met all inclusion criteria. Evaluation instruments utilized were as follows:

The Clinician Administered PTSD Scale for Children and Adolescents (CAPS-CA) is a structured clinical interview that consists of standardized prompt questions, supplementary follow-up (probe) questions, and behaviorally anchored 5 point rating scales corresponding to the frequency and intensity of each symptom assessed. It is designed to be a developmentally adjusted counterpart to the CAPS for adults (Blake et al 1995, Nader et al 1996). The CAPS-CA interview assesses the 17 symptoms for PTSD outlined in DSM-IV. It provides a means to evaluate the overall severity of PTSD as well as scores for the three symptom clusters of PTSD; re-experience, avoidance/numbing and hyperarousal. The CAPS-CA has internal consistency for the intensity ratings and concurrent validity with the Child PTSD Checklist, a self-report measure of PTSD (Nader et al 1996). Additional features to increase the utility of this instrument with children include: iconic representations of the rating scales; opportunities to practice with the format prior to questions, and a standard procedure for identification of the critical 1 month time-frame for current symptoms. A board certified child psychiatrist (VC) who was trained on the administration of the instrument conducted the CAPS-CA interview. Moreover, an intra-class correlation coefficient of .97 was established on a sub-sample of the interviews in the current sample with one of the developers of the instrument (Dr. Elana Newman) who rated videotaped recordings of ten interviews.

The PTSD Reaction Index is a 20-item self-report instrument used to assess PTSD symptoms after exposure to violence (Pynoos et al 1987, Nader et al 1990). The measure uses a five-point likert rating scale to assess frequency ranging from 'none' to 'most of the time'. The reaction index is a widely used instrument that has been shown to be a valid and reliable measure of PTSD symptoms (e.g., inter-rater reliability kappa=.88, internal consistency alpha=.78).

The Kiddie and Young Adult Schizophrenia and Affective Disorders Schedule, Present State and Lifetime (K-SADS) is a semi-structured clinical interview designed to identify Axis I DSM-IV disorders. A board certified child psychiatrist (VC) conducted the K-SADS. This instrument permitted assessment of clinical comorbidity as well as convergence between its PTSD supplement and the CAPS-CA.

The Weschler Abbreviated Scales of Intelligence (WASI) and the Weschler Intelligence Scale for Children-Third Edition (WISC-III) were used to determine intelligence (The Psychological Corporation 1999). The PTSD sample completed the WASI and control subjects completed the WISC-III. The WASI is a nationally standardized (N= 2,245) test of intelligence that yields Verbal, Performance, and Full Scale IQ scores that correlate with the subscales of the WISC-III and the Wechsler Adult Intelligence Scale - Third Edition (WAIS-III).



## 2.3 Neuroanatomical Evaluation

**2.31 MRI Acquisition**—MR data were acquired using a 1.5 Tesla G.E.-Signa scanner (General Electric, Milwaukee, Wisconsin). A coronal 3D volumetric spoiled gradient echo (SPGR) series (TR=35, TE=6, flip angle=45°; number of excitations=1, FOV=24, matrix=256×192, 124-1.5 mm. contiguous slices) was acquired on all subjects and used for all measurements and analysis. Both experimental and control groups were scanned with the same pulse sequence and the software provided compatible results (See Patwardhan et al 2001). We analyze all scan prior to processing and remove all scans that have evidence of movement artifacts.

**2.32 Volumetric Image Analysis**—MRI data were imported into the program *BrainImage 5.X* (Reiss 2002) for blinded semi-automated image processing, analyses and quantification including the utilization of a well-validated fuzzy tissue segmentation algorithm (Reiss et al 1998). As part of its procedures, the software corrects for inhomogeneities in image intensity. To define the prefrontal region, each dataset was positionally normalized so as to be perpendicular to a horizontal plane defined by the anterior (AC) and posterior (PC) commissures. The rater then selected the most rostral coronal slice containing the corpus callosum. Although neurofunctionally non-specific, this approach provides consistency across subjects in defining our area of interest. All slices anterior to this point were included in the prefrontal measurements. Left and right divisions of the prefrontal cortex were defined by the interhemispheric fissure while superior and inferior portions were demarcated in standardized proportional Talairach space (Talairach et al 1998) by a plane parallel the AC-PC plane and one-fourth the distance from the AC-PC plane to the top of the brain (Figure 1). Gray matter, white matter, and cerebrospinal fluid components of the prefrontal regions were measured using built-in functions of *BrainImage*.

Measurement of intracranial, corpus callosum, vermis, brainstem, and their component parts was based on a previously existing protocol from our laboratory (Mostofsky et al 1998b). Briefly, this protocol consists of first determining the best midsagittal slice based on clarity of the cerebellar vermis, cerebral aqueduct, corpus callosum, and spinal cord. The midsagittal slice was generated by rotating the brain in the x,y, and z, planes. The vermis was then divided into three regions of interest (ROIs) by circumscribing lobules I-V, VI-VII, and VIII-X separately, following all fissures that exceeded 2 pixels in width. Interrater reliability for these structures was calculated using a repeated measures intraclass correlation coefficient. These values were .967 for lobules I-V, .991 for lobules VI-VII, and .971 for lobules VIII-X.

To ascertain brainstem measurements, perpendicular lines were drawn that defined the midbrain-pons, the pons-medulla, and the medulla-spinal cord borders. *BrainImage* automatically generated the lines when given 5 neuroanatomic landmarks: superior and inferior pontine notches, the endpoints of the brainstem, and the tip of the foramen magnum. The superior border of the pons was defined by drawing a straight line from the superior pontine notch perpendicular to the center line axis. The inferior border was defined similarly using the inferior pontine notch. The lateral border of the pons was defined as the most lateral slice (in a sagittal view) where the pons and crus cerebri of the midbrain were connected. Interrater reliability values for the midbrain and the pons were .92 and .96, respectively.

**2.33 SPM5 Voxel-Based Morphometry Analysis**—Voxel-based morphometry (VBM) analysis was carried out using the statistical parametric mapping software, SPM5 (Wellcome Department, University College London; <http://www.fil.ion.ucl.ac.uk/spm/>) and VBM5 software (<http://dbm.neuro.unijena.de/vbm>). We created custom templates using a CCHMC pediatric template (age 5-18, both genders) ([www.irc.cchmc.org](http://www.irc.cchmc.org); Wilke et al., 2003) to create the closest approximate priors used for the segmentation when creating of the study-specific

custom priors. We then created custom priors (gray, white, and csf) by averaging all subjects' bias corrected, HMRF segmented, and normalized images, i.e. all the gray, bias corrected, HMRF segmented, and normalized images were averaged to create a gray matter prior. These custom priors were used in the final processing in lieu of the SPM default priors for segmentation. Processing steps included applying bias correction and a Hidden Markov Random Field (HMRF) model (prior probability weight 0.3), segmentation, normalization, Jacobian modulation and smoothing using an 8mm FWHM isotropic Gaussian kernel. The final resolution was 1mm<sup>3</sup>. Nineteen PTSD subjects were included in this analysis (scans from the other 5 subjects did not segment properly) and 22 controls (two controls had no IQ scores) were used in this analysis.

**2.34 Tissue Segmentation**—Both tissue segmentation and image smoothing were performed using tools identical to those described by Ashburner and colleagues (Ashburner et al 2000). All images were automatically segmented into gray, white, and cerebrospinal fluid based on signal intensity and non-brain tissue was simultaneously removed using automated SPM segmentation for T1-weighted images. A binary map of gray matter was generated from the segmentation process. In order to minimize the potential effects of noise and anatomic variance, the gray tissue was then smoothed using an 8-mm isotropic FWHM (full width, half-maximum) kernel. Images were scaled to a global mean intensity of 100 for each subject.

Average gray matter maps were created for both the control and the PTSD group and simple group contrasts were calculated. Voxel-wise paired t tests were performed in order to compare differences in gray matter density between groups using  $p < 0.05$  set as the significance threshold. In order to account for spatial correlations in the data due to multiple statistical comparisons, an extent threshold of 0.05 was used to filter out non-significant clusters of voxels (Poline et al 1995).

**2.35 Data Analyses**—To investigate volumetric differences in prefrontal gray matter volume between the PTSD and control groups, a multivariate analysis of variance was conducted using total brain gray matter volume and full-scale IQ as covariates. Since groups were matched on age and gender we did not control for these variables in our analyses of covariance (ANCOVA). The dependent variables consisted of the right superior, left superior, right inferior, and left inferior gray matter volumes of the prefrontal cortex. A joint-expected probability statistical threshold (Poline et al. 1997) of  $P = 0.01$  for height and extent while adjusting for local roughness of images (Worsley et al. 1999; Hayasaka et al. 2004) was used.

Multiple analysis of covariance (MANCOVA) was utilized to determine if the PTSD and control group had significantly different volumes for vermis subregions, corpus callosum subregions, midbrain, and pons, with intracranial area as a covariate. Following the MANCOVA, individual ANCOVAs were used for subregion comparisons to more specifically characterize group differences in brain morphology. A p-value of 0.05 (two-tailed) was chosen as the significance threshold for regions, predicted on an *a priori* basis, to be reduced in the PTSD group (intracranial, corpus callosum, vermis areas). A p-value of .01 (two-tailed) was used for exploratory analyses in which no *a priori* hypotheses were specified.

### 3. RESULTS

#### 3.1 Subject Characteristics

The mean age of the children was 11 years ( $\pm 2.24$  years), (IQ= 90  $\pm 18.66$ ). There were 14 boys and 10 girls. Ethnic composition was Euro-American (n=14), African-American (n=6), Hispanic (n=3), and Asian (n=1). Most children (83%) experienced multiple traumatic events. Traumatic events included witnessing violence (50%), physical abuse (46%), separation and loss (38%), sexual abuse (21%), physical neglect (13%), emotional abuse (13%). Comorbidity

was high (16.7%) for depression (12.5% had major depressive disorder, and 4.2% had depressive disorder, not otherwise specified), social phobia (12.5%), ADHD (12.5%), separation anxiety disorder (8%), generalized anxiety disorder (8%), and simple phobia (8%).

The control group had  $IQ = 105 \pm 10.36$ . Their mean age was 11 years ( $\pm 2.73$  years). There were 14 boys and 10 girls. Two of the subjects did not have an IQ evaluation, but were still included in this group because of lack of behavioral, cognitive or emotional difficulties and history of traumatic stress. A board certified child psychiatrist (ALR) clinically screened all subjects and corroborated no psychiatric diagnoses in this group. Ethnic composition was Euro-American ( $n=17$ ), Hispanic ( $n=5$ ), and Asian ( $n=2$ ).

### 3.2 Volumetric Image Analysis

The MANCOVA revealed a significant difference in the profile of prefrontal volume measures between subject groups (Wilks' lambda = 0.590,  $F(4,39) = 6.784$ ,  $p < 0.001$ ). Post hoc analyses of the separate ANCOVAs comprising the model revealed significant differences in all four prefrontal regions, with the most robust findings evident in the inferior portions. Left superior [ $F(1,42)=10.856$ ,  $p=0.002$ ], right superior [ $F(1,42)=4.831$ ,  $p=0.034$ ], left inferior [ $F(1,42)=19.644$ ,  $p<0.001$ ], and right inferior [ $F(1,42)=15.09$ ,  $p<0.001$ ] (See Figure 2).

Intracranial area was significantly (5.5%) smaller in the PTSD group relative to the control group ( $F=10.95$ ;  $df=1,46$ ;  $p<0.005$ ) (See Table 1). The MANCOVA Wilks' Lambda of .53 ( $F=3.16$ ;  $df=10,36$ ;  $p=0.005$ ) indicated a unique pattern of midsagittal morphological variation that distinguished children with PTSD from control subjects.

Controlling for differences in intracranial area, total and subregional corpus callosum area were not significantly different between the groups. The corpus callosum sub-division demonstrating the greatest difference in area corresponded to the splenium, where the PTSD group had a mean area reduction of 8.7% ( $F=.139$ ;  $df=1,15$ ;  $p=.71$ ).

Analysis of the brainstem showed that midsagittal area of the pons ( $F=17.424$ ,  $df=1,45$ ;  $p=.0001$ ) was significantly reduced in subjects with PTSD, while midbrain areas ( $F=.038$ ,  $df=1,45$ ;  $p=.85$ ) demonstrated no significant between-group difference.

The area of cerebellar vermal lobules I-V (anterior vermis) was not significantly different between groups; however, subjects with PTSD did show significant reductions in lobules VI-X (posterior vermis) ( $F=7.741$ ,  $df=1,45$ ;  $p=0.01$ ). The posterior vermis is further sub-divided into lobules VI-VII and VIII-X. While the groups exhibited no significant difference for lobules VI-VII, subjects with PTSD demonstrated a near significant trend for reduction in lobules VIII-X ( $F=6.994$ ,  $df=1,45$ ;  $p=0.01$ ).

There were no significant differences in brain morphology between the PTSD subgroup meeting full DSM IV diagnostic criteria and those having sub-threshold symptoms.

### 3.3 SPM Analysis

The PTSD group showed significantly greater gray matter volume compared to the control group in a large cluster within the ventral prefrontal regions with two peaks, one in the right rectal gyrus and the other in the left medial gyrus (See Figure 3). Significantly greater gray matter volume also was observed bilaterally in the occipital lobe (See Figure 4). The control group did not show significantly greater gray matter volume compared to the PTSD group. See Table 2 for z-scores, p-values and coordinates for the results of the SPM analyses.



## 4. DISCUSSION

Our findings support the hypothesis of abnormal morphological variation of specific brain regions in youth with PTSD as compared to matched healthy controls. Volumetric analysis demonstrated morphological differences between groups across all prefrontal regions examined. Specifically, the PTSD group had increased gray matter volume in superior and inferior prefrontal regions. Voxel-based analysis further localized increased gray matter density to the ventral prefrontal regions, including the rectal and medial gyri. In this manner, we have demonstrated converging evidence for abnormalities in the prefrontal regions of children with PTSD.

Increased gray matter volume may reflect a dysfunctional frontal lobe system. Functional deficits in frontal lobe pathways may lead to their failure to regulate key areas of the limbic system, such as the orbitofrontal cortex or the amygdala. These two structures have demonstrated altered activity during emotional tasks in adult PTSD fMRI studies (Shin et al 1999, Pissioti et al 2002). Larger frontal volume may not be associated with PTSD pathogenesis, but may be a risk factor that may result from activity-dependent synaptogenesis, increased arborization or decreased pruning during development. These processes could all represent risk factors for PTSD. The fact that all regions examined were significantly different by volumetric analysis may suggest a generalized process affecting all of the prefrontal region or conversely our need to develop and apply more specific methods, such as SPM.

When we examined areas in which PTSD subjects showed greater gray density than controls, via SPM analysis, increased gyrus rectus (part of the orbitofrontal cortex) and medial gyrus were observed. Adult PTSD functional studies have found that the orbitofrontal cortex (OFC) demonstrates increased activation during traumamimetic tasks (Rauch et al 1996, Fischer et al 1996, Shin et al 1997). Specifically, Rauch and colleagues using script-driven imagery technique (traumatic vs. neutral) in adults with PTSD, demonstrated increased rCBF within right-sided areas, such as the anterior cingulate and the posterior orbitofrontal areas (Rauch et al 1996). In addition, the posterior cingulate and the inferior parietal cortex in adults with PTSD have shown increase cerebral blood flow when compared to non-PTSD combat exposed adults during exposure to combat-related material. The anterior cingulate and the medial prefrontal cortex, however, demonstrated a decrease in blood flow during these traumamimetic tasks in the PTSD group (Bremner et al 1999). The different activation of the medial prefrontal cortex in these studies may be secondary to methodological issues. While Bremner and colleagues used pictures and sounds stimuli, Rauch and his group presented subjects with narratives of their traumatic events. Increased gray matter density may indicate true morphological differences. Alternatively, it may indicate more dense gray matter in one group in an area of same volume or since normalization is imperfect, there may be spatially reciprocal gray matter findings in the two groups.

Two studies in adult PTSD have found smaller anterior cingulate cortex volumes (Yamasue et al 2003, Rauch et al 2003) and, in pediatric PTSD, one group has found smaller prefrontal cortex (De Bellis et al 2002a). Our findings of increased gray matter volume and density in the prefrontal cortex stand in contrast to these findings and may indicate different methodology, such as sample selection, analysis of different regions or the separation of gray matter from white matter. In addition, adult subjects on these studies experienced different types of traumas. In Yamasue's study subjects experienced one acute terrorist act. In Rauch's study subjects were women who were exposed to emotional trauma when they worked as combat nurses in the Vietnam War. Our findings may indicate that cellular events (such as, decreased pruning) may alter the development of the prefrontal cortex and increase the risk of difficulties in the processing of traumatic experiences.

Interestingly, De Bellis has demonstrated with the use of proton magnetic resonance spectroscopy (MRS) that children with PTSD have lower levels of N-acetylaspartate (NAA) in the anterior cingulate region of the brain (De Bellis et al 2000). Decreased NAA in this region suggests neuronal loss. In this study we have no findings in the anterior cingulate region, specifically.

Our findings stand in contrast with findings in adults with Major Depression (MD) in which smaller medial orbitofrontal (gyrus rectus) volumes have been identified when compared to healthy controls (Bremner et al 2002). These reduced volumes parallel functional studies showing decreased blood flow and metabolism in adults with MD (George et al 1994).

The PTSD group also showed increased gray density in the bilateral occipital lobes. Interestingly, compared to control subjects, PTSD patients in a dissociative state (assessed by the Clinician-Administered Dissociative State Scale after a traumatic script-driven imagery symptom provocation paradigm) demonstrated more activation in the occipital and temporal gyri, along with parietal and frontal areas (Lanius et al 2002). Although dissociation is a common symptom of children with PTSD, this study did not measure dissociation and hence we cannot make any conclusions of the association between this symptom and these regions.

Of interest, a regional volumetric increase in the face of global whole brain volume deficit has been observed in other neuropsychiatric conditions affecting children. For example, in William's syndrome we find preservation of cerebellar and superior temporal gyrus volumes in an otherwise reduced brain volume (Reiss et al, 2000). In a study of adults with velo-cardio-facial syndrome increased gray matter volume in frontal and temporal clusters were found even when total brain gray volume was smaller than in matched controls (Van Amelsvoort et al 2001). These selected areas of increase gray matter volume and density, as the ones found in this study, may indicate a disruption of normal maturational changes that occur on gray matter distribution. For example, recently Sowell and colleagues, by studying a developmental cohort of children, adolescents and adults, found an inverse relationship between maps of cortical gray matter density reduction and brain growth after adolescence. Interestingly, these findings were primarily in the superior frontal regions that control executive functioning (Sowell et al, 2001). Maximum synaptic density in areas of the frontal cortex is reached by about the first year of life; exuberant synaptic connections develop until about the age of 7, followed by synapse elimination (Huttenlocker & Dabholkar 1997). Our sample may be delayed in terms of neural reorganization or may have had an accelerated growth spur in comparison to the age matched control group.

Contrary to expectations and findings from previous reports (De Bellis et al 1999a, 2002a), reductions in total or subregional corpus callosum areas were not detected in the present study. Similar to the study by De Bellis and colleagues, we found the region of greatest corpus callosum reduction in the PTSD group to be localized to the posterior segment containing the splenium (De Bellis et al 1999a). However, the mean reduction of 8.7% (as compared to De Bellis and colleagues study showing 11.8%) did not reach statistical significance when covaried for intracranial area. Differences in results could be accounted by methodological variation. For example, De Bellis' study divided the corpus callosum into 7 sub-divisions, as opposed to 5 in this study. Sample size also could account for the inconsistency in corpus callosum findings. De Bellis and colleagues evaluated a larger sample of children with PTSD symptoms (N=44) than studied here (N=24).

The reduced area of the pons in subjects with PTSD is of interest because this structure is responsible for the main noradrenergic response to stress (via the locus coeruleus in the dorsal pons) (Bremner et al 1996). Underdevelopment of the pons may also result in a lack of regulation of this structure via afferent innervation and a resulting exaggerated response to

stress. Of interest, in view of our results in the cerebellar vermis, brainstem malformations have been associated with cerebellar maldevelopment (Patel and Barkovich 2002).

The observed reduction in posterior vermis area in PTSD adds to increasing evidence that abnormal vermal morphology is characteristic of many psychiatric and neurodevelopmental conditions such as bipolar disorder (DeBello et al 1999), ADHD (Mostofsky et al 1998a), autism (Courchesne et al 1988; Haas et al 1996; Levitt et al 1999), and schizophrenia (Nopoulos et al 1999; Supprian et al 2000). The importance of the vermis in emotion regulation had been demonstrated by patients with isolated, cerebellar vermal disease, who are commonly found to have personality changes involving flattening of affect (Rapoport and Inoff-Germain, 2000; Schmahmann and Sherman 1998). Some core PTSD symptoms, such as emotional numbing also contain components of affective flattening, suggesting the possibility of a common neuroanatomical substrate.

It also is important to note the specificity of our vermal findings. While the posterior vermis was reduced in area, anterior vermis area was preserved in the PTSD group. The posterior vermis has been shown to play a role in the modulation of non-motor behavior with its extensive projections to regions playing key roles in mood regulation (Anand et al 1959). A lesion study in rhesus monkeys found that posterior vermal lesions differed from those in anterior vermal location by their association with more dramatic changes in behavior (Berman et al 1978). In humans, it is known that neurogenetic disorders with serious behavioral implications such as Joubert and fragile X syndrome, have decreased posterior vermal areas (Guerreiro et al 1998; Holroyd et al 1991; Mostofsky et al 1998b). Subjects with these two syndromes typically possess social and communication problems resembling autistic behavior (Reiss et al 1995; Holroyd et al 1991). Conversely, subjects with Williams syndrome, who are unusually socially outgoing and overly friendly (Jones et al 2000), show significant increases in the posterior vermis and neocerebellar hemispheres relative to normal controls (Jernigan and Bellugi 1990; Wang et al 1992; Schmitt et al 2001). Thus, there is support for the hypothesis that aberrant neural functionality involving the cerebellar vermis may play a role in alterations in affect and social behavior in children with PTSD.

Areas of the pons, corpus callosum and cerebellar vermis have a growth spur from about age 1 to 4, then they grow exponentially until they reach their adult size by around age 10 (Hayakawa et al 1989). Hence, interpretation of our results must take into consideration that the sample may be undergoing maturational changes at the time of the study.

By utilizing morphometric voxel-based analysis in PTSD, this study extends the use of this methodology in pediatric psychiatry. This study is strengthened by its relatively large sample size and control group matched for age and gender. It is limited, however, by its cross-sectional design and lack of ethnicity and SES matching. Although we controlled for IQ, cognitive differences between the two groups may represent other disparities between the two groups that were not assessed in this study, such as psychosocial deprivation. Although no different in terms of functional impairment, volumetric findings or cortisol levels (Carrion et al 2001, Carrion et al 2002a, Carrion et al 2002b), other unknown biological disparities between the PTSD and sub-threshold groups could impact the results. Although lessened by the use of two different methods, technique specific artifacts may influence the findings. Since SPM does have a tendency toward type II errors (Missimer et al 1999), this study utilized another independent method and demonstrated convergence of results. Our results will need to be replicated and extended with studies incorporating a longitudinal design, and standardized assessment of social environment as well as same IQ measures. Future studies should also control for current intervention at time of evaluation, for both pharmacologic or psychotherapy. Qualifiers of the trauma should also be assessed, for example, age of trauma onset may play a role in how early life stress affects brain development.

The understanding of PTSD pathogenesis will help elucidate the pathway from biological proclivity to psychopathology. Voxel-based morphometry of the brain is likely to be one of several useful tools as we investigate the progression of diathesis to environmental stress to symptom and ultimately to syndrome in the developing brain and in adults. In this report we present data suggesting increased prefrontal gray matter volume and density in children with PTSD symptoms when compared to healthy controls. We also report reduced areas in the pons and the posterior vermis when controlling for intracranial area. These structures may be associated with some of the cardinal symptoms of PTSD, such as physiological hyperarousal and emotional numbing. It will be important to continue assessing prefrontal cortex and midsagittal structures along with other regions of interest (ie: hippocampus) when conducting volumetric studies. Future investigations will target regions of interest, such as the prefrontal cortex, through the use of experimental tasks in fMRI. Efforts to develop tasks that elicit functional alterations in pediatric PTSD are underway.

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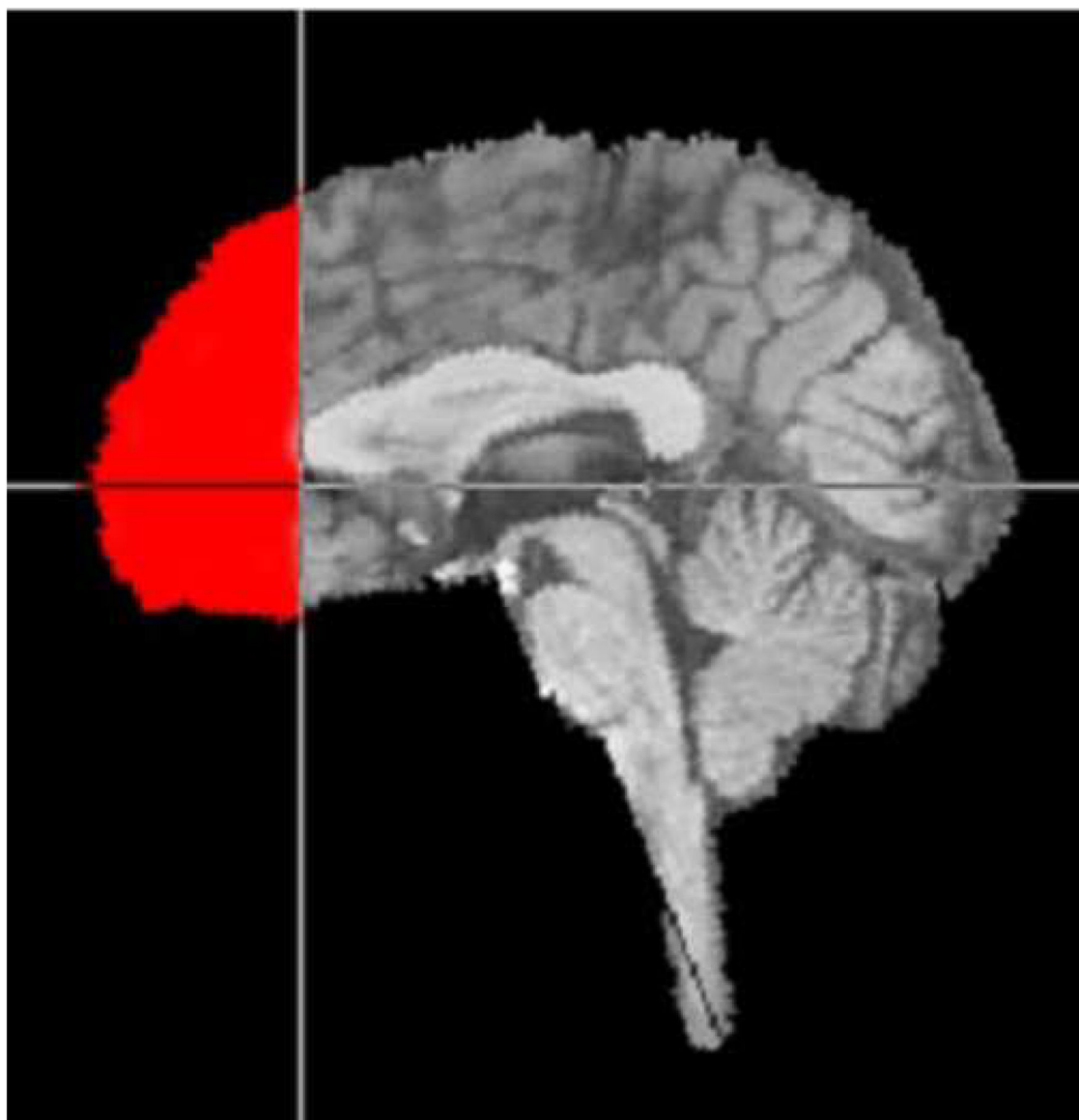
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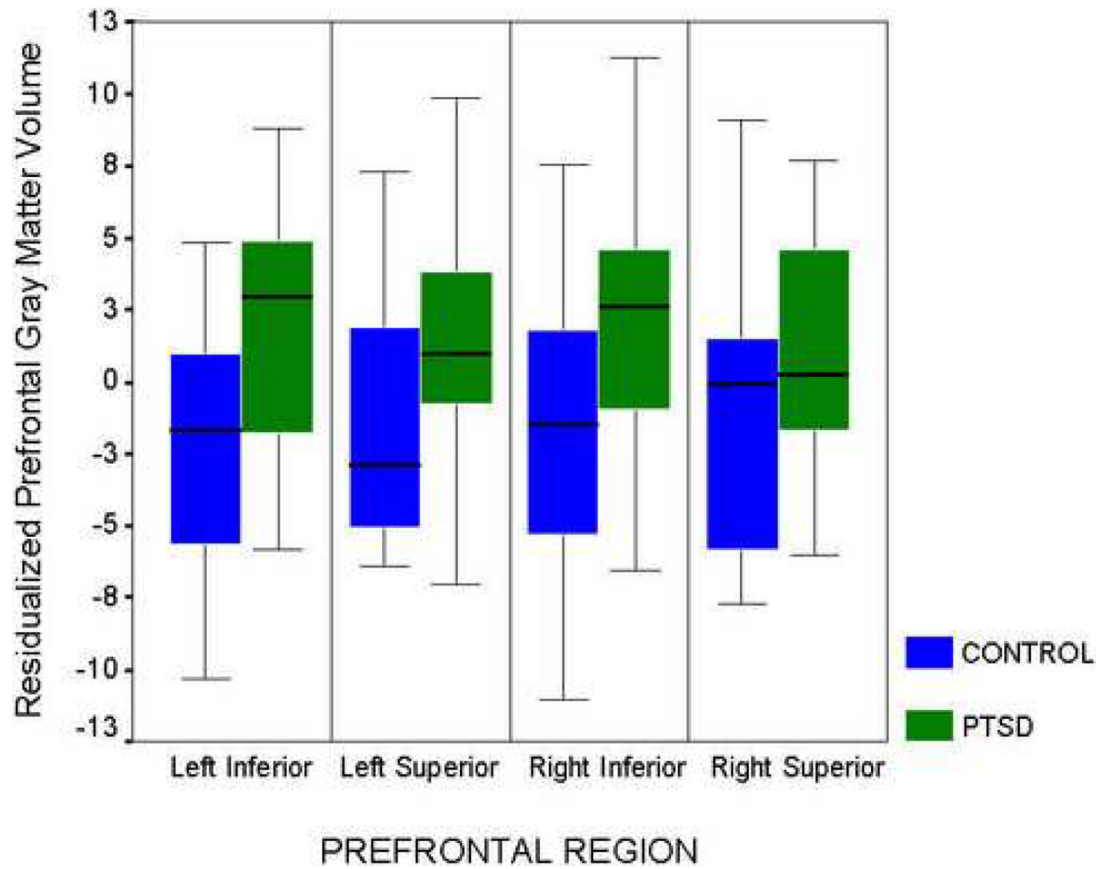
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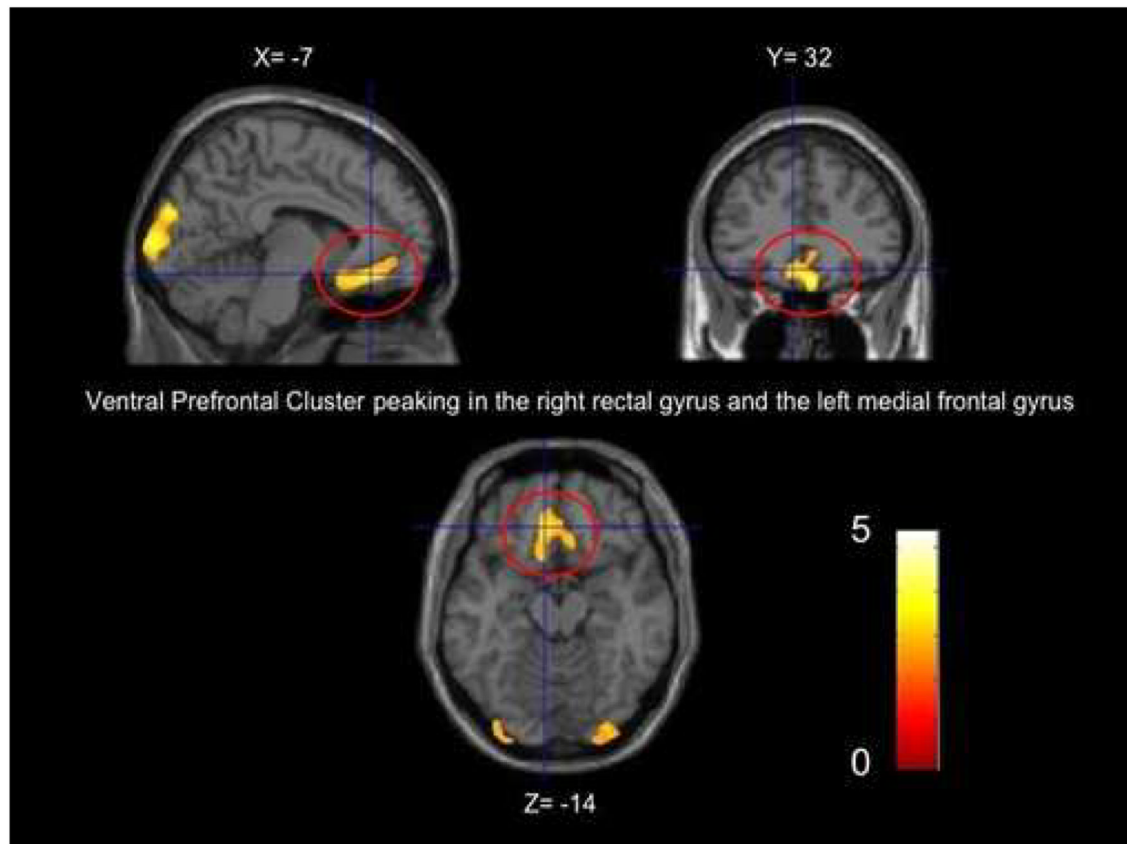


**Figure 1.**  
Posterior demarcation of the PFC anterior to most rostral coronal slice containing the corpus callosum



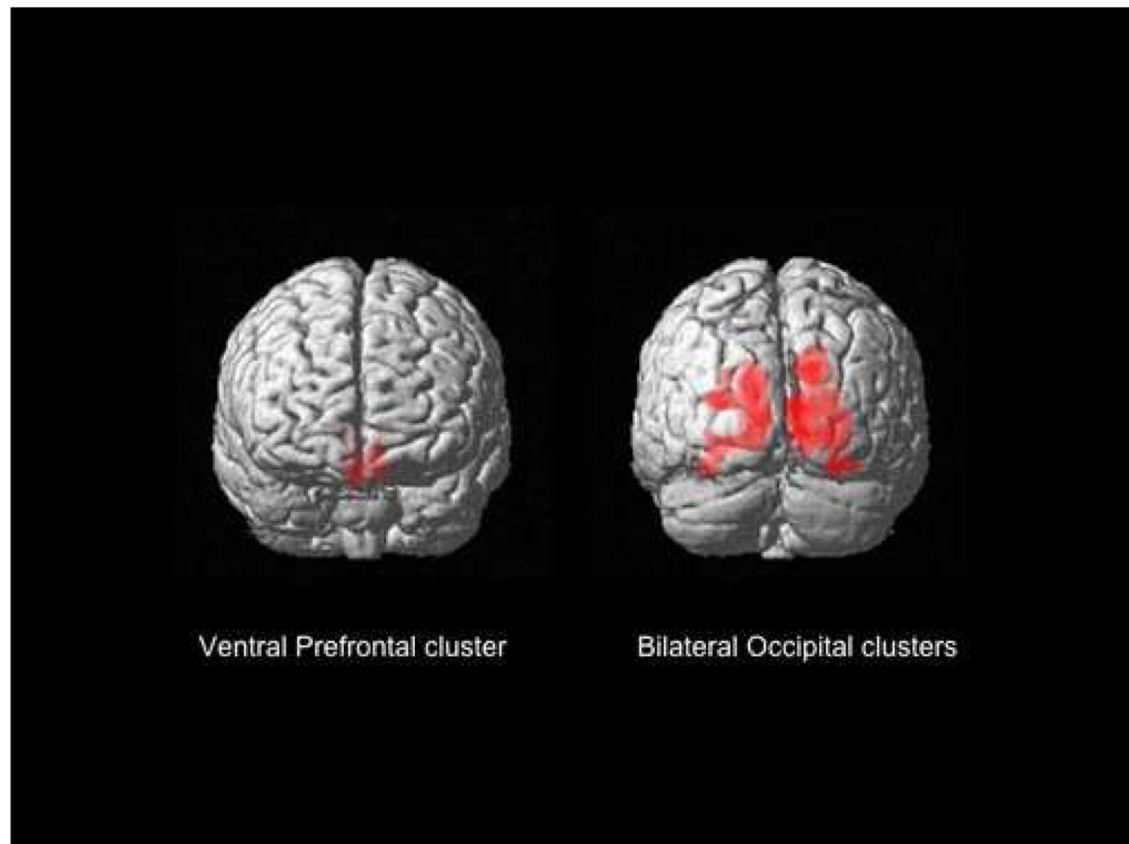
**Figure 2.**  
Prefrontal volumes of PTSD and control groups in four prefrontal cortex regions





**Figure 3.**

PTSD group shows increase gray matter density in ventral prefrontal regions  
 Relative gray matter density preservations in PTSD compared to typically developing controls as shown by the PTSD - control contrast surface renderings. The global height threshold of  $p=0.01$  and extent threshold of  $p=0.01$ .



**Figure 4.**

PTSD group shows increased gray matter volume in ventral prefrontal and occipital lobe regions.

Greater gray matter in PTSD is shown by the PTSD-control contrast surface renderings. The global height threshold of  $p=0.01$  and extent threshold of  $p=0.01$ .

TABLE 1

Midsagittal Measurements

		Control group (n=24)	PTSD group (n=24)	p values	F values
intracranial area		156.9±8.3	148.3±9.8	0.0018 <sup>a</sup>	10.948
corpus callosum area		7.19±1.04	6.57±0.94	0.3487 <sup>b</sup>	0.897
	segment 1_splenium (posterior)	1.83±0.24	1.67±0.29	0.7108 <sup>b</sup>	0.139
	segment 2	1.14±0.20	1.06±0.21	0.4038 <sup>b</sup>	0.710
	segment 3	1.18±0.18	1.08±0.17	0.9033 <sup>b</sup>	0.015
	segment 4	1.32±0.25	1.21±0.24	0.6671 <sup>b</sup>	0.187
	segment 5_genum (anterior)	1.74±0.33	1.62±0.19	0.7924 <sup>b</sup>	0.070
vermis area		12.85±1.33	11.4±1.40	0.017 <sup>b</sup>	6.141
	I-V (anterior vermis)	5.28±0.47	4.80±0.78	0.1583 <sup>b</sup>	2.058
	VI-VII	3.51±0.57	3.14±0.47	0.0535 <sup>b</sup>	3.931
	VIII-X	4.06±0.54	3.51±0.51	0.0112 <sup>b</sup>	6.994
	VI-X (posterior vermis)	7.57±1.0	6.65±0.73	0.0089 <sup>b</sup>	7.471
midbrain area		3.17±0.21	2.97±0.40	0.8459 <sup>b</sup>	0.038
pons area		6.22±0.46	5.29±0.66	0.0001 <sup>b</sup>	17.42

Areas are measured in cm<sup>2</sup>

Analysis of intracranial area was performed with one-way analysis of variance (ANOVA) using diagnosis (PTSD vs. Control subjects) as a between-subject factor. Analysis of covariance (ANCOVA) was used for subregion comparisons to more accurately quantify group differences after adjusting for the effect of total brain volumes.

<sup>a</sup> ANOVA

<sup>b</sup> ANCOVA with intracranial area as a covariate

**Table 2**

Z-scores, p-values and coordinates for results of the SPM analyses

Activated Regions	P value (corrected)	# of Voxels	Z Score (maximum)	Peak location Talairach coordinates x y z
PTSD - control				
Right cuneus, middle occipital gyrus	<0.001	10894	4.59	10 -96 2
Left inferior and middle occipital gyrus, cuneus	<0.001	10481	4.12	-37 -88 -12
Right rectal gyrus, left medial frontal gyrus	0.009	5867	3.71	4 31 -19