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Decreased Prefrontal Cortical Volume Associated With Increased Bedtime Cortisol in Traumatized Youth

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Abstract

Background—The purpose of this study was to investigate prefrontal cortex (PFC) volumes in youth with posttraumatic stress disorder symptoms (PTSS) and explore the relationship between cortisol secretion and PFC volumes.

Methods—Total brain tissue volumes, segmented areas of the PFC and diurnal cortisol secretion were examined in a sample of 33 youth aged 10–16 years. Cerebral volumes were available for 45 subjects (30 PTSS and 15 Controls).

Results—Youth with PTSS had significantly decreased total brain tissue and total cerebral gray volumes in comparison to healthy controls. While controlling for total cerebral gray volume, the PTSS group demonstrated decreased left ventral and left inferior prefrontal gray volumes. A significant negative association was found between pre-bedtime cortisol levels and left ventral PFC gray volumes for the full sample.

Conclusions—Findings suggest associations between posttraumatic stress and PFC neurodevelopment. Findings also suggest a link between PFC development and cortisol secretion.

Keywords

prefrontal cortex; cortisol; posttraumatic stress; sMRI; developmental traumatology; child maltreatment

Introduction

Studies of individuals with prefrontal cortex (PFC) lesions have shown that abnormalities of the PFC can lead to difficulties with attention, memory and emotion regulation (1). Children with posttraumatic stress symptoms (PTSS) demonstrate difficulties in these areas,

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²The distribution of time passed since participants traumatic experienced in this sample did not allow for an examination of the role of time since the trauma on the relation between cortisol levels and PTSD symptoms.

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supporting investigation into PFC structure and development (2,3). Through hormonal signals, environmental experiences such as severe psychological trauma can influence synaptogenesis, arborization and pruning early in neurodevelopment (4). Since the PFC is one of the last regions to mature, this region may be specifically affected by adverse conditions during early childhood.

Environmental stress activates a cascade down the limbic-hypothalamic-pituitary-adrenal (LHPA) axis that leads to an increase in cortisol secretion (5). Limbic and frontal regions rich in glucocorticoid receptors may be particularly sensitive to cortisol effects (6). Past studies have shown increased levels of cortisol in youth with maltreatment-related PTSS (7,8). Specifically, we have found pre-bedtime cortisol levels to be significantly higher in youth with PTSS when compared to healthy controls (9). In addition, hierarchical linear modeling analysis in the current PTSS sample demonstrated a curvilinear trend with relatively higher evening levels when compared to healthy controls (10). Animal studies have indicated that in response to increased exposure to stress hormones the PFC may undergo abnormal structural changes (11).

The objectives of this study are as follows: (1) to replicate the finding that children with PTSS would demonstrate decreased total brain tissue volume and cerebral gray volumes when compared to healthy controls (HC); (2) to test the hypothesis that children with PTSS would demonstrate altered PFC volumes when compared to HC; and (3) to determine whether there is a negative correlation between cortisol secretion and PFC volumes, specifically in PFC regions showing differences between groups.

Methods and Materials

Participants

A total of 33 subjects underwent imaging and cortisol assessments. Structural MRI data was collected in 12 additional subjects in this sample for a total of 45 (30 PTSS and 15 HC). Please refer to Table for sample characteristics. Inclusion criteria included; 1) age between 10-16, 2) medication-naïve, 3) history of interpersonal trauma and a score of 10 or greater on the Clinician Administered PTSD Scale, Child and Adolescent Version (CAPS-CA) for the PTSS group¹. Exclusion criteria consisted of a history of alcohol or drug dependence, mental retardation, gross obesity or growth failure, autism or schizophrenia, neurological disorder, fetal drug exposure, or significant medical illness.

Measures

To assess PTSS symptoms, we used the CAPS-CA (12). The Schedule for Affective Disorders and Schizophrenia for School-Age Youth-Present and Lifetime Version (K-SADS-PL), was utilized to assess comorbid Axis I psychiatric disorders (13). The Wechsler Abbreviated Scales of Intelligence (WASI) was used to assess IQ (14). Youth also completed The Child PTSD Symptom Scale (CPSS) (15) and the Child Behavior Checklist (CBCL) (16) as screening measures for control participants. If control participants endorsed symptoms of PTSS consistent with clinical levels they were not included in the study. Participants' pubertal development was determined by self-report (17).

Salivary cortisol data was obtained from our previous study of cortisol dysregulation (10). Thirty-three participants (19 PTSS and 14 controls) also provided MRI data, hence only these subjects were included in the analysis of associations. Based on our previous findings

¹We employed this strategy of examining youth exposed to significant trauma and who experience PTSD symptoms versus using only youth who meet full diagnostic criteria to be consistent with our previous study and because research suggests limitations to the DSM-IV criteria in youth.

we utilize pre-bedtime cortisol levels as the primary variable of interest given this value's sensitivity to PTSS and the relative elevation of cortisol levels at this time when compared to HC (10). For participants who completed two or three days of collection cortisol levels were averaged and skew in the distribution of pre-bedtime cortisol was corrected with a square root transform. Participants with only a one day sample were not included. Details on salivary cortisol collection methods and reliability can be found in our previous report (10).

MRI Acquisition

MRI data were collected using a 3 tesla G.E. signa scanner (General Electric, Milwaukee, WI). A high resolution, T1-weighted coronal, three-dimensional, spoiled grass gradient echo (SPGR) series with the following parameters was collected for each participant (TR = 35 ms, TE = 6 ms, flip angle 45 degrees, number of excitations = 1, field of view = 24 cm, matrix = 256×192 , 124 1.5mm contiguous slices in a coronal plane, with a spatial resolution of $1.5\text{mm} \times 0.9 \times 0.9$ per slice).

Image Analysis

All individuals involved with processing and measuring the imaging data were assessed for reliability in this process, and were kept blind to group membership. Raw data were processed using *Brainimage 5.x* (18).

To isolate the PFC, whole brain images were uniformly positioned along a horizontal plane defined by landmarks on the anterior and posterior commissures by a rater (KR), who was blind to diagnostic status. A coronal slice containing the initial appearance of the anterior corpus callosum was selected to mark the posterior boundary of the PFC. The PFC was divided into dorsal, superior, inferior, and ventral regions proportionally using a plane orthogonal to the interhemispheric fissure and parallel to the plane defined by the anterior and posterior commissures (see Figure 1). Tissue in each region was divided in right and left and measured in cubic centimeters.

Results

Preliminary Descriptive Analyses

Comparison of the PTSS and HC on demographic variables, pubertal status and handedness is presented in the Table. Groups did not significantly differ on age, gender, ethnicity, handedness, or Tanner stage. Healthy controls, however, had higher median family incomes and higher IQ scores than the PTSS group.

Hypothesis Testing

PTSS participants had significantly smaller total brain tissue and cerebral gray volumes than HC (see Table). Both left and right cerebral gray were significantly smaller in the PTSS group. ANCOVAs with total cerebral gray volume as a covariate indicated that left ventral PFC ($F(1, 42) = 4.95, p < .032$) and left inferior PFC gray volumes ($F(1, 42) = 4.75, p = .035$) significantly differ across the two groups. Means and standard errors are presented in the Table.

Given the findings that left ventral gray and left inferior volumes significantly differed across the two groups, we examined the association between pre-bedtime cortisol level and PFC left ventral and left inferior gray matter. Mean pre-bedtime cortisol levels were 0.093 ($SD = 0.08$) in the PTSS group and 0.056 ($SD = 0.03$) in the control group. For this analysis, given the reduced sample size, the two groups were combined to increase power, giving a mean of 0.078 ($SD = 0.07$). Moreover, CAPS-CA scores were not correlated with left ventral or left inferior gray volumes. Cortisol was significantly negatively related to left

ventral PFC gray volumes ($r(31) = -.43$; $p = .013$ (two tailed) depicted in Figure S1 (see Supplement), suggesting that relatively increased cortisol levels were associated with relatively lower PFC left ventral gray matter (the correlation with left inferior was ($r(31) = .30$, $p = .088$). The correlation between cortisol and left ventral PFC by group: control group ($r(12) = -.46$; $p = .102$) and in the PTSS group ($r(17) = -.43$; $p = .066$).

Given that IQ significantly differed across the PTSS and control groups and the potential role of age we explored the pattern of unique associations between age, full scale IQ, cortisol levels and left ventral gray and left inferior gray volumes using a series of regression analyses. Detailed results are available from the first author and indicated that while controlling for either age or IQ, cortisol was still significantly negatively related to left ventral PFC gray volumes.

Discussion

The data replicate findings of decreased total brain tissue and cerebral gray volumes in youth with PTSS (2,3). The PTSS group also demonstrated significantly decreased left ventral and left inferior volumes. There was a negative correlation between pre-bedtime cortisol levels and left ventral PFC volumes.

The results suggest that cortisol secretion may have an effect on the development of the PFC. Although we utilized the complete sample to increase power, this decision was supported by findings that the medial PFC in humans has a high glucocorticoid receptor density (6). Further, the fact that both groups demonstrate similar negative correlations, support our rationale to combine both groups; cortisol effects on the PFC may not be a function of PTSS. However, youth with PTSS may have a more detrimental exposure to this hormone (9,10) and thus more negative effects on brain development (i.e., the smaller volumes demonstrated in this study and elsewhere (2,3). Larger sample studies should continue to address this question.

As these are cross-sectional results, interpretation of findings must be cautious. A limitation of our study is the disparity in the socioeconomic status (SES) between groups. Disparities in SES have been shown to alter prefrontal function in children from low SES backgrounds (19). Our data analysis, however, demonstrated no correlation between SES and ventral or inferior PFC volumes. In addition, if SES had an effect on total cranial gray matter, we have controlled for this variable in our analyses. Longitudinal studies with pre-trauma and post-trauma designs are needed to more comprehensively determine the association between cortisol secretion and PFC development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Division of the PFC into dorsal, superior, inferior, and ventral regions

Table
Comparison of PTSS and Control Groups on Study Variables

	Controls (n=15)	PTSS (n=30)
IQ and Demographic Variables		
Mean Age (SD)	13.3 (1.8)	13.2 (2.2)
Gender		
% Female	26.7	33.3
Median Tanner Stage (SD)	3.7 (0.9)	3.3 (1.4)
Ethnicity %		
White	73.0	53.3
African American	0.0	3.3
Hispanic	0.0	23.3
Pacific Islander	6.7	0.0
Other	20.3	19.9
Handedness		
% Right Handed	92.9	87.0
Weschler IQ Score (SD)	120.5 (7.2)	110.1 (14.8)
Median Family Income **	100,000-125,000	50,000-75,000
Total Cerebral Volumes		
	Mean (Std. Error)	Mean (Std. Error)
Total Tissue *	1370.25 (107.7)	1314.71 (96.1)
Total Gray *	786.44 (63.3)	750.74 (55.6)
Left Gray *	395.74 (34.7)	378.63 (27.5)
Right Gray *	390.70 (29.4)	372.12 (29.3)
PFC Gray Volumes		
	Mean (Std. Error)	Mean (Std. Error)
Left Superior	18.77 (0.77)	19.28 (0.54)
Right Superior	20.51 (0.90)	20.89 (0.63)
Left Inferior **	32.56 (1.02)	29.80 (0.72)
Right Inferior	33.24 (1.07)	31.19 (0.75)
Left Dorsal	4.99 (0.41)	5.37 (0.29)
Right Dorsal	5.65 (0.47)	5.99 (0.33)
Left Ventral **	15.63 (0.89)	13.19 (0.62)
Right Ventral	15.16 (0.87)	13.39 (0.61)

* significant difference (no covariate, one tailed test)

** Significant difference (two tailed test); PFC sub region means are covariate (total cranium gray) adjusted.