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Stress Predicts Brain Changes in Children: A Pilot Longitudinal Study on Youth Stress, Posttraumatic Stress Disorder, and the Hippocampus

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ABSTRACT

OBJECTIVE. Does stress damage the brain? Studies of adults with posttraumatic stress disorder have demonstrated smaller hippocampal volumes when compared with the volumes of adults with no posttraumatic stress disorder. Studies of children with posttraumatic stress disorder have not replicated the smaller hippocampal findings in adults, which suggests that smaller hippocampal volume may be caused by neurodevelopmental experiences with stress. Animal research has demonstrated that the glucocorticoids secreted during stress can be neurotoxic to the hippocampus, but this has not been empirically demonstrated in human samples. We hypothesized that cortisol volumes would predict hippocampal volume reduction in patients with posttraumatic symptoms.

PATIENTS AND METHODS. We report data from a pilot longitudinal study of children ($n = 15$) with history of maltreatment who underwent clinical evaluation for posttraumatic stress disorder, cortisol, and neuroimaging.

RESULTS. Posttraumatic stress disorder symptoms and cortisol at baseline predicted hippocampal reduction over an ensuing 12- to 18-month interval.

CONCLUSIONS. Results from this pilot study suggest that stress is associated with hippocampal reduction in children with posttraumatic stress disorder symptoms and provide preliminary human evidence that stress may indeed damage the hippocampus. Additional studies seem to be warranted.

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Key Words

stress, child maltreatment, cortisol, MRI, hippocampus

Abbreviations

PTSD—posttraumatic stress disorder
DSM-IV—*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*

CAPS-CA—Clinician-Administered PTSD Scale for Children and Adolescents
CSF—cerebrospinal fluid

HPA—hypothalamic-pituitary-adrenal

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FOR MORE THAN a decade, a medial temporal brain structure named the hippocampus, because of its sea-horse shape, has been studied in the pathophysiology of posttraumatic stress disorder (PTSD). The hippocampus' functional role in memory processing and its anatomic location (part of the limbic system) has made this structure a prime candidate for investigation in relation to PTSD because the disorder is characterized by intrusive recollections of the traumatic event and difficulties with emotion regulation. Research into the neurobiology of PTSD has been aided by the availability of high-resolution MRI, which has made it possible to obtain accurate volumetric measurements of the hippocampus. The literature reports significantly reduced hippocampal volumes in adults with PTSD when compared with healthy controls.¹⁻⁵ These findings have not been replicated when investigating the hippocampal volume of children with PTSD.⁶⁻⁸ These studies have found either no difference between PTSD and controls in hippocampal volume^{6,7} or larger hippocampal volumes secondary to larger volumes of white matter, but no gray matter.⁸

The relationship between the hippocampus and PTSD remains to be determined because many questions are unresolved. Why have findings failed to replicate in youth? Are the identified volumetric abnormalities of the hippocampus in this condition a risk factor for developing symptoms of PTSD or are the structural differences a biological marker of stress for this behaviorally defined disorder? Pathophysiological differences between adult and pediatric PTSD may, in part, be explained by clarifying the role of stress in human hippocampal development.

The hippocampus has a protracted ontogeny, persistent postnatal neurogenesis, and a high density of glucocorticoid receptors.⁹⁻¹¹ An increasing body of research suggests that stress and the glucocorticoids secreted by the adrenal steroids during stress can damage the hippocampus.^{12,13} This damage includes alteration of pyramidal cell morphology, pyramidal cell death, and suppression of granule cells.^{14,15} These stress-mediated hippocampal changes can also be induced by injection of corticotropin-releasing factor.¹⁵ Because of our work¹⁶ and others¹⁷ documenting high levels of cortisol in children with PTSD, we reasoned that it would be important to study the associations among cortisol levels, PTSD symptoms, and hippocampal volume changes in children with a history of traumatic stress. We have found that prebedtime salivary cortisol levels demonstrated the largest difference in values between children with PTSD and controls (ie, it seems to be the best marker of pathogenic cortisol levels).

The risk-versus-marker question remains unanswered because to date, most of the studies examining hippocampal volume have been cross-sectional in design. De Bellis and colleagues¹⁸ assessed hippocampal

volumes in 9 prepubertal maltreated children and 9 healthy controls at baseline and after 2 years' follow-up. They found no differences in hippocampal changes between groups at baseline, follow-up, or across time. They noted, however, that left hippocampal volume decreased across time in both groups, and that this may have been influenced by the sample's postpubertal status. Group comparisons may have been underpowered and may not have adequately explored hippocampal change within the PTSD group. Such groups of youth are often quite heterogeneous.

Given the above findings, we theorized that hippocampal volume reductions in adults may result in part from chronic exposure to stress throughout childhood development. A lifetime accumulation of stress effects on the hippocampus would help explain the positive volumetric findings in adults and the lack of findings in younger samples. The impact of chronicity was studied by Wignall and colleagues¹⁹ who found smaller right hippocampal volumes in adults with recent-onset PTSD after acute trauma, suggesting that either hippocampal damage occurs within months of the trauma or that smaller hippocampal volume is a predisposing factor for PTSD. When examined longitudinally, however, individuals with acute trauma assessed at baseline and who developed PTSD 6 months later ($n = 10$) did not differ from those individuals who did not develop PTSD ($n = 27$) in terms of hippocampal size at either baseline or at follow-up.²⁰ This suggests that smaller hippocampal volume is not a risk factor for developing PTSD after an acute event. In a pivotal monozygotic twin study, Gilbertson and colleagues²¹ compared twins who were discordant for chronic trauma (Vietnam combat) exposure. They found that unexposed co-twins of those with PTSD also had smaller hippocampi, suggesting that smaller hippocampal volume is a preexisting familial vulnerability factor. Although this study does not rule out the possibility of an added toxic environmental effect, they note that those siblings with combat-exposure did not have any additional reduction of their hippocampal volumes.

Differences between findings in adult and pediatric studies regarding hippocampal volume may also be attributed to neuromaturational factors. Early life stress may alter synaptogenesis, dendritic proliferation, and pruning, but these effects may not manifest until later development. For example, preclinical studies have shown that differences in hippocampal synaptic density arise in rats exposed to early stress only postpubertally as a consequence of attenuated synaptogenesis.²²

On the basis of the theory that the changes in hippocampal volume found in the adult PTSD brain result from prolonged exposure to neurotoxic levels of cortisol secreted during chronic stress, we conducted a longitudinal study of children with history of traumatic stress who already show signs and symptoms of PTSD. This

evaluation entails behavioral, endocrinological, and neuroanatomical (via structural MRI) assessment at baseline (time 1) and follow-up (time 2; 12–18 months later). Drawing from the existing literature and our hypothesis that hippocampal volume reductions may result, in part, from chronic exposure to stress throughout childhood development, we hypothesized that PTSD symptoms and cortisol levels would be associated with changes in hippocampal volumes across time 1 to time 2. We focused on prebedtime cortisol levels (for the reason noted above) and total PTSD symptoms and explored the specific role of hyperarousal symptoms (cluster D). Of the 3 clusters of PTSD [reexperience (B), avoidance and numbing (C), and hyperarousal (D)], we have found D to be highly pathognomonic of PTSD in childhood and a strong predictor of later impairments.^{23–25}

PATIENTS AND METHODS

Participants

Participants were recruited from local departments of social services and mental health clinics, and all of the participants fulfilled the following criteria: (1) at least 1 episode of exposure to trauma, as defined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (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”;²⁶ (2) age 7 to 13 years old; (3) a severity score of ≥ 12 on the PTSD Reaction Index. Exclusion criteria consisted of a history of mental retardation; history of schizophrenia or autism, presence of any metal or electrical conductive implants or foreign bodies; and current history of substance dependence and history of clinically significant head trauma, epilepsy, or other documented neurologic disorder. Most children experienced multiple traumatic events. Traumatic events included witnessing violence, physical abuse, separation and loss, sexual abuse, physical neglect, and emotional abuse.

The sample consisted of 6 boys and 9 girls, for a total sample of 15 children. The mean age of the children was 10.4 years, with a range of 8 to 14 years. In terms of family income, 47% reported incomes between 0 and \$21 000, 27% reported incomes between \$21 000 and \$41 000, and 13% of the families reported incomes over \$41 000 (2 families did not report income). Ethnic composition was white ($n = 7$), black ($n = 6$), Hispanic ($n = 1$), and Asian ($n = 1$). Children’s average pubic hair Tanner stage was 2.1; for girls average breast Tanner stage was 2.0, for boys average genital Tanner stage was 2.1. Wechsler Abbreviated Scale of Intelligence full-scale IQs ranged from 62 to 142, with an average score of 89.0. (Two participants scored below 70. These participants were included in the sample because they had no

previous history of mental retardation and were able to participate in the clinical evaluation).

Clinical Evaluation

All participants and their legal guardians were presented with an institutional review board-approved informed consent and agreed to participate. An in-depth clinical evaluation was conducted on all referred children with an PTSD Reaction Index score ≥ 12 .

Evaluation Instruments

To assess PTSD symptoms, we used the Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA).²⁷ The CAPS-CA is a developmentally sensitive counterpart to the CAPS for adults.²⁸ This clinical interview consists of standardized prompt questions, supplementary follow-up (probe) questions, and behaviorally anchored 5-point rating scales corresponding with the frequency and intensity of each symptom assessed. The CAPS-CA assesses all DSM-IV criteria for PTSD. Specifically, it assesses exposure to criterion A1 events and the individuals’ experience of these events (ie, criterion A2), the 17 symptoms for PTSD clustered in DSM-IV (ie, criteria B, C, and D), and the 1-month duration requirement (criterion E). The frequency and intensity of each of the symptoms were rated via behaviorally anchored ratings (0–4 for frequency and 0–4 for intensity) and then summed. The CAPS-CA has good internal consistency estimates for the ratings and has shown concurrent validity with the Child PTSD Checklist.²⁹ A certified child psychiatrist (Dr Carrion) who was trained on the administration of instrument conducted all CAPS-CA interviews. The following variables were computed with the CAPS-CA: (1) total traumatic stress symptoms and (2) hyperarousal symptoms: a composite score of ratings from the 5 hyperarousal items from symptom cluster D.

Biological Maturation

Participants’ pubertal development was determined by self-report. Participants selected from drawings with written descriptions representing the 5 Tanner stages³⁰ of pubic hair development and genital development for boys and breast development for girls. Previous research has demonstrated that self-report Tanner staging is a valid and reliable method that has been shown to correlate with physician ratings.³¹

Neuroendocrine Evaluation

Salivary Cortisol

Cortisol samples were obtained from the participant during home-based measurements. They were collected 4 times a day (prebreakfast, prelunch, predinner, and prebedtime) over the course of 3 consecutive days producing 12 samples. Detailed instructions were provided

to caretakers and children regarding the collection of saliva samples. Samples were collected by placing a cotton swab in the participant's mouth for 1 minute. The cotton was then placed inside a sterile plastic tube, sealed, and kept refrigerated. Saliva was extracted from the cotton by centrifuging the plastic tubes and cotton for 8 to 10 minutes. The cotton was then removed and the tubes sealed. All samples were kept at -20°C and shipped on dry ice to the laboratory for assay. Samples were processed using the Magic Cortisol radioimmunoassay kit produced by Ciba-Corning (Giessen, Germany) as adapted for salivary cortisol analysis by the University of Minnesota Endocrine Laboratory.³² Interassay and intraassay coefficients of variation are maintained at $<12\%$. Cortisol is reported in micrograms per deciliter. As recommended for increased reliability,³³ an aggregate score (mean) from the 3 days was created for each time period, and to reduce the number of statistical tests we used the mean cortisol level for the aggregated cortisol levels for analyses in this investigation. Individuals showed relative stability in their cortisol levels across the 3 days. Specifically, the correlation between day 1 and day 2 mean cortisol level was ($r = 0.46$; $P < .001$) between day 1 and day 3 ($r = 0.52$; $P < .001$) and day 2 and day 3 ($r = 0.31$; $P < .001$). Prebedtime cortisol was the primary variable used on the basis of our previous findings identifying this value as the largest difference between children with PTSD and healthy controls.¹⁶

Neuroanatomical Evaluation

MRI Acquisition

MRI data were acquired using a 1.5-T GE-Signa scanner (General Electric, Milwaukee, WI). Coronal 3-D volumetric spoiled gradient echo series (repetition time: 35 milliseconds; echo time: 6 milliseconds; flip angle: 45° ; number of excitations: 1; field of view: 24; matrix: 256×192), and 124- to 1.5-mm contiguous slices were acquired on all participants and were used for all measurements and analysis.

Image Analysis

Morphometric analysis was performed at the Center for Interdisciplinary Brain Sciences Research at Stanford University and was conducted by research staff blind to the hypothesis in this study and the PTSD status of the participant. Volumetric assessment of segmented image data in the software program, BrainImage,³⁴ requires a stepwise process of data importation, removal of non-brain voxels, correction of image nonuniformity, positional normalization, and fuzzy tissue segmentation. The assessment of hippocampus volumes in BrainImage required a manual delineation of regions of interest. Brain tissue was isolated, and coronal images were oriented perpendicular to the anterior commissure-posterior commissure plane. Interrater reliability testing was performed

between 2 well-trained raters blind to diagnoses to ensure accuracy in measurements. A single rater then circumscribed regions of the hippocampus for all participants on coronal images oriented perpendicular to the anterior commissure-posterior commissure plane and according to a protocol previously developed in our laboratory.³⁵ To increase the resolution at which the regions of interest could be drawn, the matrix sizes of the coronal data sets were expanded from 256 to 512×10^2 pixels by using a bicubic interpolation algorithm. The image contrast was increased so that the amygdala and hippocampus were clearly distinguishable from the surrounding white matter and cerebrospinal fluid (CSF). Volume measures recorded total tissue and were examined separately for right and left volumes. The anterior-most slice of the hippocampus was determined by the presence of the alveus and by the development of a laminar structure that distinguishes the hippocampus from the amygdala. The borders were defined by the surrounding white matter and CSF and superiorly by the amygdala. The hippocampus excluded the tail of the caudate nucleus anteriorly and excluded the thalamus posteriorly. Circumscription of the hippocampus continued until it disappeared posteriorly, approximately at the point where the corpus callosum fuses with the fornix. Time 1 and time 2 hippocampal volumes were highly correlated (left $r = 0.89$; right $r = 0.85$).

Statistical Methods

The association between changes in hippocampal volumes and PTSD symptoms was examined by using Pearson correlations, and between hippocampal volumes and cortisol were examined by using Spearman correlations because of the nonnormal distribution of prebedtime cortisol levels using unidirectional tests at ($P < .05$). The association was examined using a 2-stage process. The change in volume was first calculated by simple subtraction of time 1 volumes from time 2 volumes. Thus, positive numbers represented increases in volume and negative numbers decreases in volume. In addition to testing simple change values, we also conducted a more stringent test of the associations among cortisol, PTSD symptoms, and hippocampal development. Specifically, we examined change in hippocampus volumes from time 1 to time 2 while controlling for biological maturation (Tanner stage) and gender. To do this, a change variable was computed by calculating the standardized residuals of time 2 hippocampus volumes predicted by Tanner stage, gender, and time 1 hippocampus volumes via regression analyses. These standardized change scores thus represent the difference in expected time 2 hippocampal volume on the basis of Tanner stage, gender, and time 1 hippocampus volumes. Positive scores represent a relative increase, whereas negative scores represent a relative decrease. This technique and the unidirectional tests, as opposed to a multiple linear

regression strategy for example, were chosen to balance type 1 and 2 error rates because of the relatively small sample size. Specifically, using a single regression analysis (as opposed to our 2-stage process) with 4 predictors only leaves 9 degrees of freedom, making it virtually impossible to detect a significant effect with the present sample size (in other words, it inflates type 2 error beyond reasonable expectations). With a sample size of 14 or 15, this sets as “significant” findings where the association explains 20% or more of the covariance, a fairly large effect size for these type of studies, thus balances type 1 (ie, conclude there is an effect when there is none) and type 2 error (ie, conclude there is not an effect when there is one).

RESULTS

Examination of the score ranges and skew indicated that cortisol levels were not normally distributed and that there was 1 significant outlier in change in right hippocampus volumes (the score was a full SD increase from the next closest increase). This case was excluded from the analyses. Descriptive statistics for the variables of interest are presented on Table 1.

As noted, hippocampal change and residualized change were computed such that a negative number indicates a decrease in predicted volume over time. Correlations among the measures of PTSD symptoms, cortisol, and hippocampal change are presented in Table 2 and indicated that the severity of PTSD symptoms and the cortisol levels at time 1 were significantly negatively correlated with change in right hippocampus volumes using both the simple change score, as well as the residualized change score. No significant correlations were found for change in left hippocampus volumes. The association between residual change in right hippocampal volumes and PTSD symptoms and cortisol levels are depicted in Fig 1.

Exploratory analyses were conducted to determine whether hippocampal volumes at time 1 were associated with change (calculated similarly as hippocampus change) in PTSD symptoms from time 1 to time 2, and

TABLE 2 Summary of Correlations Between Hippocampal Change, Time 1 Cortisol Levels, and Time 1 PTSD Symptom Severity

	Total PTSD	Hyperarousal	Cortisol ^a
Left hippocampal time 1	0.05	0.34	-0.29
Right hippocampal time 1	0.29	0.56 ^b	-0.37
Left hippocampal time 2	-0.03	0.18	-0.53 ^c
Right hippocampal time 2	0.13	0.32	-0.35
Simple right hippocampal change	-0.58 ^c	-0.68 ^d	-0.48 ^c
Residualized right hippocampal change	-0.46 ^c	-0.46 ^c	-0.50 ^c
Simple left hippocampal change	-0.17	-0.38	-0.14
Residualized left hippocampal change	-0.24	-0.16	-0.40 ^e

^a Correlations with cortisol are Spearman rank-order correlations.

^b Not significant with a directional test.

^c $P < .05$.

^d $P < .01$.

^e $P = .08$, 1-tailed.

results indicated that this association was not statistically significant ($r = -0.04$; $P = .45$).

DISCUSSION

Our results support the hypotheses that PTSD symptoms and cortisol levels at baseline are associated with changes in hippocampal volume over an ensuing 12- to 18-month interval. Specifically, we found that severity of PTSD symptoms and cortisol levels predict a reduction in hippocampal volume from baseline to follow-up when controlling for pubertal maturation and gender in children with a history of traumatic stress. This is the first longitudinal study in PTSD to document an association between hippocampal changes with PTSD symptoms and with a marker of stress, cortisol levels. These longitudinal findings help elucidate previous cross-sectional reports of smaller hippocampal volumes in PTSD populations. Our results are also in accord with animal literature reporting on the neurotoxic effects of glucocorticoids in the hippocampus. Our results stand in contrast, however, with studies identifying hippocampal volume as a vulnerability factor. Although, this study was not designed to address the vulnerability factor hypothesis, our exploratory analyses suggest that hippocampal volume was not a risk factor for development of PTSD symptoms.

Participants with the highest severity of PTSD symptoms, and more specifically hyperarousal symptoms, had a reduction of their hippocampal volume. Behavioral manifestations of the syndrome may have direct developmental effects on a brain structure involved in managing cognitive processes. In past research, we have found that hyperarousal symptoms in children with PTSD predict the development of cognitive difficulties in this syndrome.²⁴ Such findings may help elucidate the reasons for cognitive impairment in PTSD, and this mechanism speaks to the inherent chronicity of the disorder because less cognitive resources could jeopardize recovery from PTSD.

TABLE 1 Descriptive Statistics

	Mean (SD)	Median	Range
Total PTSD symptoms	41.00 (22.71)	38.0	6 to 80
Hyperarousal symptoms	12.00 (8.57)	15.0	0 to 25
Cortisol	0.13 (0.18)	0.06	0 to 0.7
Left hippocampal time 1	3.31 (0.50)	3.3	2.4 to 4.1
Right hippocampal time 1	3.48 (0.53)	3.3	2.9 to 4.8
Left hippocampal time 2	3.36 (0.44)	3.4	2.5 to 4.1
Right hippocampal time 2	3.63 (0.50)	3.6	2.9 to 4.9
Simple left hippocampal change	0.06 (0.24)	0.05	-0.5 to 0.4
Residualized left hippocampal change	0.00 (0.89)	0.3	-1.5 to 1.5
Simple right hippocampal change	0.10 (0.24)	0.1	-0.3 to 0.5
Residualized right hippocampal change	-0.15 (0.70)	-0.3	-1.1 to 1.0

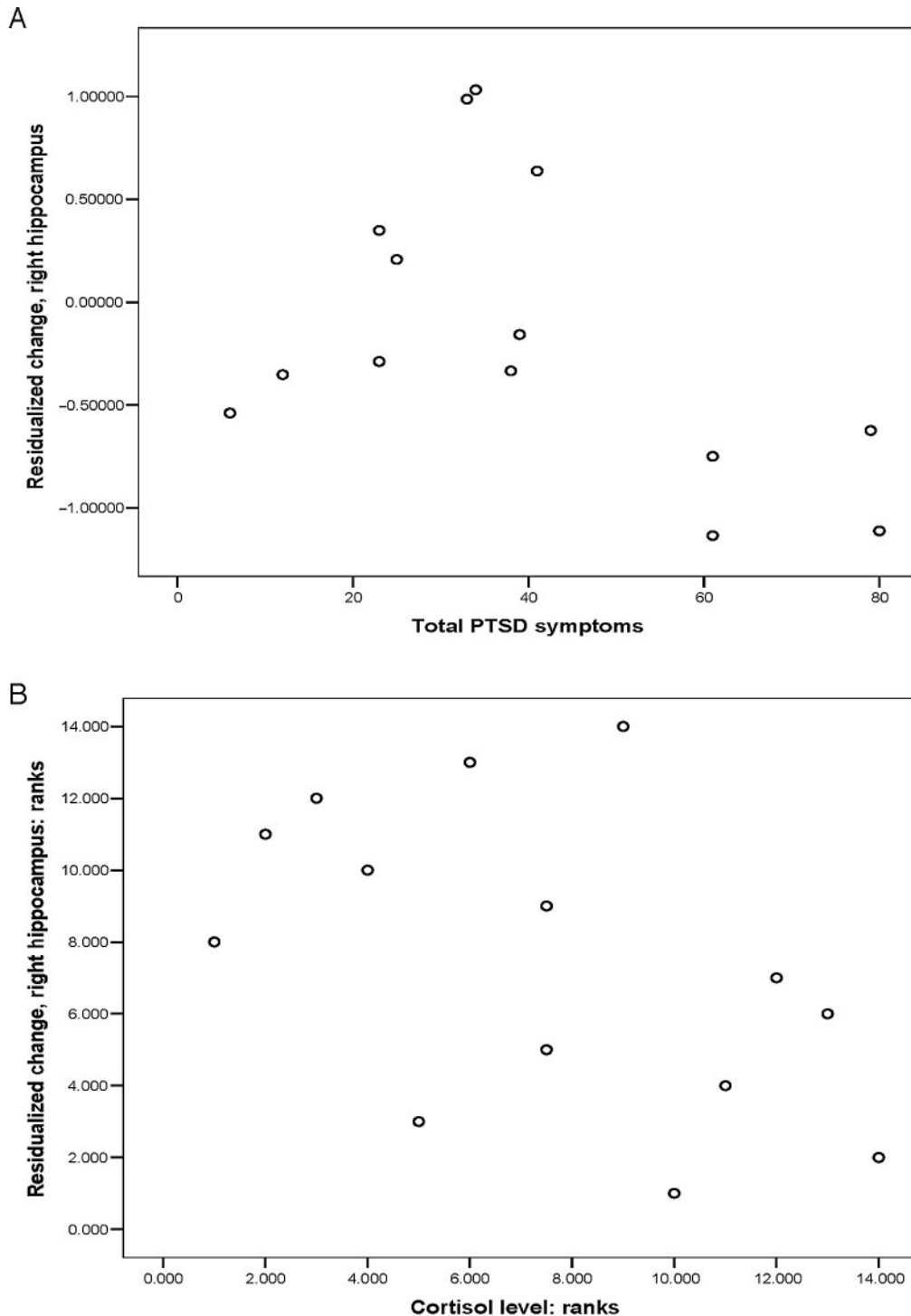


FIGURE 1 Scatterplot depiction of association between residualized change in right hippocampal volumes with PTSD symptoms and cortisol level.

Theoretically, PTSD symptoms can enhance stress in a variety of ways. For example, by interfering with the normal sleep cycle and with emotion regulation, hyperarousal symptoms may overactivate the stress-response system. This increase in noradrenergic and adrenaline response, as well as in activity of the hypothalamic-

pituitary-adrenal (HPA) axis, which results in cortisol secretion, may strain the system into what has been referred to as an allostatic load.³⁶ This allostatic load can have a direct effect on the function of these stress-response systems by altering their specificity to respond on exposure to additional stress.³⁷

Our cortisol findings address a potential mechanism by which stress can alter the hippocampus. There is substantial animal literature demonstrating the neurotoxic effects of glucocorticoid in the glucocorticoid receptor-rich hippocampus.^{14,38,39} Glucocorticoids can also exert their neurotoxicity indirectly via accumulation of extracellular glutamate.⁴⁰ High levels of glucocorticoids have been reported in children with history of maltreatment and PTSD.^{16,17} Elevated cortisol levels suggest that high levels of stress lead to activation of the HPA axis and cortisol production and that this leads to hippocampal toxicity, which results in poor inhibitory activity from the hippocampus unto other centers, such as the HPA axis itself. The putative neurotoxic effects of cortisol on the hippocampus may depend on at least 3 factors: (1) the developmental stage of the structure (the hippocampus glucocorticoid receptors density may change throughout development), (2) the level and sustainability of cortisol released, and (3) the severity and/or chronicity of the stressful events.

Most studies in adults that have found a reduced hippocampal volume in PTSD have studied populations with chronic symptoms or chronic trauma (Wignall et al¹⁹ is an exception). A longitudinal study on acute trauma and PTSD found no hippocampal differences.²⁰ Although our participants were children, their histories of severe, chronic maltreatment may have already caused enough stress early in life, so that these hippocampal changes can be identified. On the other hand, Gilbertson and colleagues²¹ who were also studying individuals with chronic history (Vietnam combat) did not find support for the theory of environmental toxicity from stress. The time since trauma, however, may also impact the volume of the hippocampus. Although the participants continue to have symptoms of PTSD, there may exist enough time for the plasticity of the hippocampus to undergo at least partial recovery. Such a conclusion is consistent with animal models of hippocampus plasticity.⁴¹ The interactions between stress vulnerability factors and markers of stress neurotoxicity are complex and may not operate in an all or none fashion.

In addition to the possibilities that a small hippocampus is a marker of PTSD or that a small hippocampus is a vulnerability factor for PTSD, other alternatives that are consistent with our findings should be considered. For example, independent of PTSD status, a small hippocampus may be a marker of chronic or ongoing stress. In addition, there can exist genetic and/or familial risk factors for enhanced vulnerability to the neurotoxic agents from stress. Finally, there can be a synergistic effect between a small hippocampus and the environmental neurotoxicity of stress. Our data could support all of these possibilities, with the exception of a small hippocampus being solely a risk factor for PTSD.

The answer to the role of the hippocampus in PTSD is

complex. This study reports on an association between stress, cortisol, PTSD, and hippocampal change that starts early in life. Although this sample represents the largest longitudinal study of hippocampal volumes in traumatized youth to date, the study and range of conclusions about additional confounding variables is limited by the sample size and findings should be considered preliminary until replicated. However, future structural imaging studies should conduct longitudinal investigations in individuals at risk for trauma before and after experiencing trauma and PTSD symptoms. It will be important to be able to accurately measure trauma type and duration, as well as duration of PTSD symptoms.

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