

Corticostriatal-Limbic Gray Matter Morphology in Adolescents With Self-reported Exposure to Childhood Maltreatment

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Objective: To study the relationship between self-reported exposure to childhood maltreatment (CM) and cerebral gray matter (GM) morphology in adolescents without psychiatric diagnoses.

Design: Associations were examined between regional GM morphology and exposure to CM (measured using a childhood trauma self-report questionnaire for physical, emotional, and sexual abuse and for physical and emotional neglect).

Setting: University hospital.

Participants: Forty-two adolescents without psychiatric diagnoses.

Main Outcome Measures: Correlations between childhood trauma self-report questionnaire scores and regional GM volume were assessed in voxel-based analyses of structural magnetic resonance images. Relationships among GM volume, subtypes of exposure to CM, and sex were explored.

Results: Childhood trauma self-report questionnaire total scores correlated negatively ($P < .005$) with GM volume

in prefrontal cortex, striatum, amygdala, sensory association cortices, and cerebellum. Physical abuse, physical neglect, and emotional neglect were associated with rostral prefrontal reductions. Decreases in dorsolateral and orbitofrontal cortices, insula, and ventral striatum were associated with physical abuse. Decreases in cerebellum were associated with physical neglect. Decreases in dorsolateral, orbitofrontal, and subgenual prefrontal cortices, striatum, amygdala, hippocampus, and cerebellum were associated with emotional neglect. Decreases in the latter emotion regulation regions were also associated with childhood trauma self-report questionnaire scores in girls, while caudate reductions (which may relate to impulse dyscontrol) were seen in boys.

Conclusions: Exposure to CM was associated with corticostriatal-limbic GM reductions in adolescents. Even if adolescents reporting exposure to CM do not present with symptoms that meet full criteria for psychiatric disorders, they may have corticostriatal-limbic GM morphologic alterations that place them at risk for behavioral difficulties. Vulnerabilities may be moderated by sex and by subtypes of exposure to CM.

Arch Pediatr Adolesc Med. 2011;165(12):1069-1077

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AN ESTIMATED 3.7 MILLION children are assessed for childhood maltreatment (CM) each year in the United States; because many cases do not come to professional attention, this likely is an underestimate

*For editorial comment
see page 1133*

of the number of children experiencing maltreatment.¹ Increasing evidence suggests that these children may endure long-lasting neural consequences of CM that place them at risk for behavioral and psychiatric sequelae. Converging data sup-

port adverse effects of early life stress on morphologic development of corticostriatal-limbic structures.²⁻⁴ Magnetic resonance imaging studies⁵⁻¹⁴ show decreased corticostriatal-limbic gray matter (GM) volume in children and adults reporting exposure to CM. Gray matter changes in the intervening adolescent epoch can also be inferred. However, few investigations focus on the neurobiological effects of CM in adolescents.

Corticostriatal-limbic GM volume decreases are well established in adults reporting CM. Hippocampus has been the region most studied in adults reporting exposure to CM, consistently demonstrating volume decreases.^{5,8-10,13,15} Volume reductions in prefrontal cortex (PFC),

striatum, and amygdala have also been demonstrated in studies^{8-12,16} of adults reporting CM. Furthermore, pre-clinical CM models implicate more widespread corticostriatal-limbic involvement,^{3,16,17} suggesting that a whole-brain approach may be especially helpful in revealing distributed CM effects. Neuroimaging investigations of CM have largely assessed adults with psychiatric diagnoses, especially posttraumatic stress disorder (PTSD) and borderline personality disorder, limiting the ability to ascertain whether brain changes are related to CM, the disorders, or both. This research also often focused on CM broadly, hindering the determination of the effects of subtypes of CM.

There are fewer imaging investigations of children exposed to maltreatment. Decreases in PFC volume observed in pediatric samples with PTSD secondary to CM suggest that some PFC changes observed in adults with CM may have originated in childhood.¹⁸ However, some regional GM differences between pediatric and adult manifestations of CM are also suggested. For example, investigations of children reporting CM do not show the hippocampal volume decreases that are prominent in adults. It has been suggested that this may be a result of delayed expression of the effects of CM in this brain region.^{14,19} Similar to investigations in adults, studies in children have been performed largely in samples with PTSD and have not investigated the effects of subtypes of abuse or neglect.

Associations between CM and GM volume in adolescents are implicated, but few studies focus on adolescents. Adolescents have been included in some pediatric investigations, often analyzed together with prepubertal children. A 2010 study²⁰ of adolescents reporting general early-life adversities, ranging from experiencing physical neglect and emotional abuse to witnessing domestic violence to having a life-threatening injury, showed decreases in hippocampus volume. This suggests that some GM differences found in adults, such as those in hippocampus, may be expressed by the time of adolescence. To our knowledge, no prior study has focused on adolescents reporting CM and used a whole-brain approach to assess distributed brain effects.

Similarities and differences in the sequelae of different types of abuse and neglect are unknown but could indicate differing vulnerabilities and the need for different detection and intervention approaches.²¹ Although physical abuse and sexual abuse have been associated with increased depression risk,^{22,23} evidence increasingly suggests that emotional maltreatment may also influence the development of negative self-associations and depression.²⁴⁻²⁸ Furthermore, hippocampal and striatal alterations in adults have been associated with reported childhood emotional neglect,^{9,29} suggesting that such neglect may have long-lasting effects on corticostriatal-limbic regions subserving emotion regulation. Sex differences may also modify the effects of CM on corticostriatal-limbic morphology. Sexually dimorphic development of stress-sensitive corticostriatal-limbic regions³⁰⁻³³ has been suggested to contribute to sex differences in psychiatric disorders, such as in regions subserving emotions and in increased depression risk in females, and in regions subserving impulse control and in increased risk for substance abuse in males.³⁴⁻³⁹

In this morphometric structural magnetic resonance imaging study, we used a whole-brain approach to study the regional distribution of GM volume differences associated with self-reported CM in adolescents without psychiatric diagnoses. We hypothesized that CM severity would be inversely associated with volume in distributed corticostriatal-limbic GM regions, including PFC, striatum, amygdala, and hippocampus. Furthermore, we hypothesized that different subtypes of maltreatment would be associated with varying regional patterns of GM reductions, with emotional maltreatment associated with reductions in corticostriatal-limbic regions subserving emotion regulation. We also performed exploratory analyses by sex. We anticipated that GM volume reductions in corticostriatal-limbic brain regions subserving emotion regulation would be associated with CM exposure in girls, while GM volume reductions in regions subserving impulse control would be associated with CM exposure in boys.

METHODS

Participants included 42 adolescents (age range, 12-17 years; mean [SD] age, 15.33 [1.37] years; 50% female; and 19 white, 19 African American, and 4 of >1 race/ethnicity) without *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) Axis I diagnoses, confirmed by the revised Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version 2.0 administered to participants and their parents or guardians.⁴⁰ Participants were recruited from a sample of children identified at birth to be at high risk for CM and followed up longitudinally by L.C.M. Additional participants were also recruited from the greater New Haven, Connecticut, community, allowing for a sample of adolescents reporting a spectrum of CM severity. Participants had no history of neurological illness, head trauma with loss of consciousness, or major medical disorder. Written informed consent was obtained from parents or guardians, and assent was obtained from minors, in accord with requirements by the institutional review board of the Yale University School of Medicine.

Participants completed the Childhood Trauma Questionnaire (CTQ),^{41,42} a self-report questionnaire on experience of the following 5 subtypes of maltreatment in childhood: physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse. *Physical abuse* is defined as bodily assaults on a child by an older person that pose a risk of or result in injury (eg, “People in my family hit me so hard that it left me with bruises or marks”). *Physical neglect* is defined as failure of caregivers to provide for a child’s basic physical needs, including food, shelter, safety, supervision, and health (eg, “I didn’t have enough to eat”). *Emotional abuse* is defined as verbal assaults on a child’s sense of worth or well-being or as any humiliating, demeaning, or threatening behavior directed toward a child by an older person (eg, “People in my family said hurtful or insulting things to me”). *Emotional neglect* is defined as failure of caretakers to provide basic psychological and emotional needs, such as love, encouragement, belonging, and support (eg, “People in my family felt close to each other”). *Sexual abuse* is defined as sexual contact or conduct between a child and an older person (eg, “Someone tried to make me do sexual things or try sexual things”). Participants rated items on the CTQ using a 5-point scale ranging from “never true” to “very often true.” Each CTQ subscale has 5 items, so subscale scores range from 5 (no maltreatment) to 25 (severe maltreatment). The 5 CM subtype scores are summed for a CTQ total

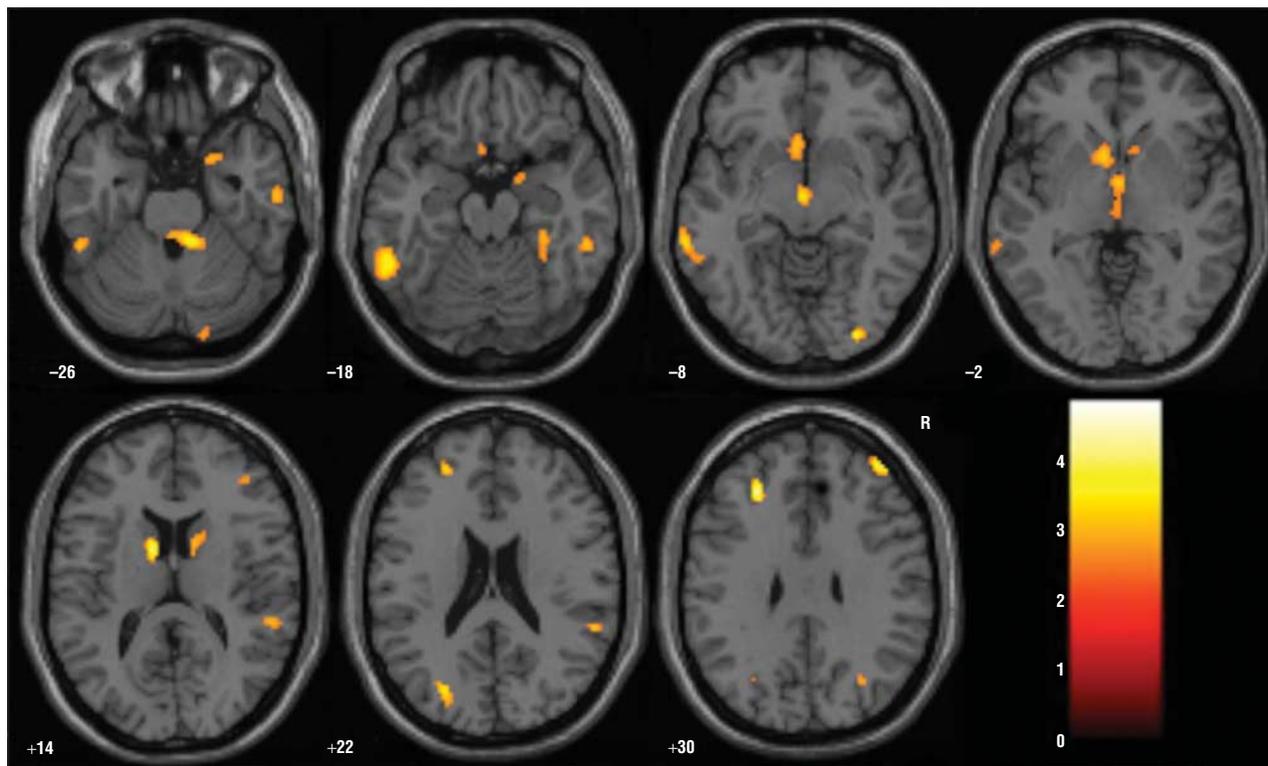


Figure 1. Decreases in gray matter associated with exposure to childhood maltreatment. Shown are regions where gray matter volume was inversely correlated with Childhood Trauma Questionnaire total scores (uncorrected $P < .005$ and cluster size of ≥ 50 voxels). The color bar shows t statistics and the numbers in white in the lower left corner of each image show the Montreal Neurological Institute z-plane coordinates (in millimeters).

score. All but 6 participants reported some form of CM, defined as a score of 6 or higher on any of the 5 CM subtype scores. Physical abuse was reported by 16 participants, physical neglect by 18, emotional abuse by 23, emotional neglect by 34, and sexual abuse by 6.

t Tests were used to examine possible sex differences in age and in CTQ total and subscale scores. Commercially available software was used (Statistical Package for the Social Sciences for Windows, version 11.1; SPSS, Inc, Chicago, Illinois).⁴³

High-resolution structural magnetic resonance images were obtained on a 3-T imaging system (Trio; Siemens, Erlangen, Germany) using a 3-dimensional magnetization-prepared rapid-acquisition gradient-echo T1-weighted sequence (repetition time, 1500 milliseconds; echo time, 2.83 milliseconds; field of view, $256 \times 256 \text{ mm}^2$; matrix, 256×256 pixels; 1.0-mm sagittal sections without gap; 160 sections; and 2 excitations). Images were processed with freely available software (Statistical Parametric Mapping 5 [http://www.fil.ion.ucl.ac.uk/spm]) using a previous protocol.⁴⁴ Briefly, the Statistical Parametric Mapping 5 segmentation function was used for bias correction, segmentation, and spatial normalization. The modulated GM images were spatially smoothed using an 8-mm full-width-at-half-maximum gaussian kernel.

Whole-brain linear regression analysis was performed in Statistical Parametric Mapping 5, covarying for age, to investigate the relationship between the CTQ total scores and GM volume. Additional regression analyses of CTQ subscale scores and GM volume were performed only for participants who reported the maltreatment subtype of CM. Separate exploratory regression analyses of the CTQ total scores were performed for female participants and for male participants. Results were considered significant at $P < .005$ (uncorrected) and cluster size of at least 50 voxels.

RESULTS

Girls and boys did not differ significantly in age, CTQ total scores, or CTQ subscale scores. The CTQ total score showed significant inverse correlation with GM volume for the following: bilateral dorsolateral PFC (DLPFC) (Brodmann area [BA] 46/9), bilateral rostral PFC (RPFC) (BA 10), left subgenual PFC (sgPFC) (BA 25), bilateral striatum and right amygdala, as well as left parietal (BA 40/7) and right temporoparietal (BA 22/40) association cortices, bilateral temporal cortex (BA 20/21), right fusiform gyrus (BA 20/37), bilateral occipital association cortex (BA 18/19), bilateral cerebellum, and regions of hypothalamus and midbrain (**Figure 1**).

The CTQ subscale scores showed inverse association with GM volume for the following self-reported variables: (1) for physical abuse, left DLPFC (BA 46/9), left RPFC (BA 10), right orbitofrontal cortex (OFC) (BA 47), right ventral striatum, right insula, and right temporal association cortex (BA 20/21) (**Figure 2A**); (2) for physical neglect, left RPFC (BA 10), right parietal association cortex (BA 40/39), and bilateral cerebellum (**Figure 2B**); and (3) for emotional neglect, bilateral DLPFC (BA 46/9), bilateral RPFC (BA 10), bilateral dorsal anterior cingulate cortex (BA 24/32), right superior frontal gyrus (BA 8), right OFC (BA 47), bilateral sgPFC (BA 25), bilateral striatum, bilateral amygdala and hippocampus, left parietal association cortex (BA 40), right temporal association cortex (BA 20/38), left occipital association cortex (BA 18/19), bilateral cerebellum, and regions of hy-

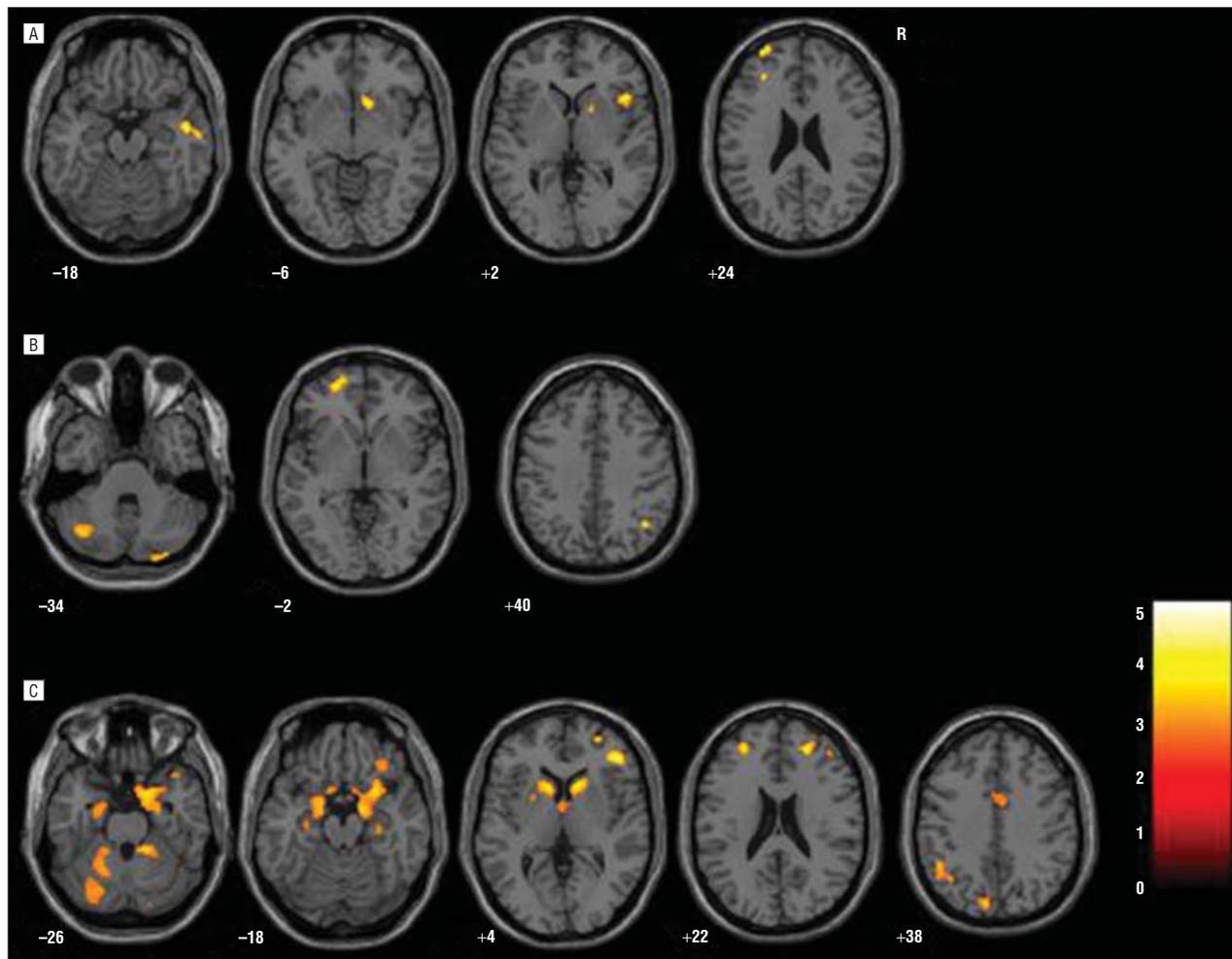


Figure 2. Decreases in gray matter associated with exposure to subtypes of childhood maltreatment. Axial-oblique views show regions where gray matter volume was inversely correlated with Childhood Trauma Questionnaire subscale scores (uncorrected $P < .005$ and cluster size of ≥ 50 voxels) for physical abuse (A), physical neglect (B), and emotional neglect (C). The color bar shows t statistics and the numbers in white in the lower left corner of each image show the Montreal Neurological Institute z -plane coordinates (in millimeters).

pothalamus and midbrain (Figure 2C). No significant results were found for emotional abuse or for sexual abuse.

In girls, the CTQ total scores were inversely correlated with GM volume in right RPF (BA 10), bilateral OFC (BA 11/47), bilateral sgPFC (BA 25/32), bilateral amygdala and hippocampus, right insula, bilateral temporal association cortex (BA 20/21/38), bilateral fusiform gyrus (BA 20), right temporo-occipital association cortex (BA 37/19), left occipital association cortex (BA 18/19), and bilateral cerebellum (Figure 3A). In boys, the CTQ total scores were inversely correlated with GM volume in bilateral caudate, bilateral temporoparietal cortex (BA 37/40), and left temporo-occipital association cortex (BA 37/19) (Figure 3B). There was a trend toward an inverse association with left RPF (BA 10) in boys; at 44 voxels, the cluster size was beneath the study threshold.

COMMENT

Our results indicate that self-reported exposure to CM is associated with reductions in GM volume in a distributed corticostriatal-limbic system, including DLPFC, RPF,

sgPFC, striatum, amygdala, and hippocampus, as well as parietal, temporal, and occipital association cortices and cerebellum. These findings were observed in a sample of adolescents without psychiatric diagnoses. Although preliminary, results of exploratory analyses support prominent reductions in RPF volume common across physical abuse, physical neglect, and emotional neglect CM subtypes, as well as patterns of additional regional GM volume decreases in the CM subtypes. Findings in girls were in regions associated with emotion regulation, whereas findings in boys were in regions subserving impulse control.

Rodent and nonhuman primate models of CM show morphologic alterations in PFC, striatum, amygdala, and hippocampus.⁴⁵⁻⁵⁴ The mechanisms that underlie these changes are unclear; acute influences of stress on corticostriatal-limbic morphologic development demonstrated in the basic models include epigenetic effects on the hypothalamic-pituitary-adrenal axis, dysregulated functioning of neurotransmitter and intracellular signaling pathways, and reductions in neurotrophic factors and neurogenesis.^{3,50-54} These morphologic changes are associated with behavioral changes, including increased im-

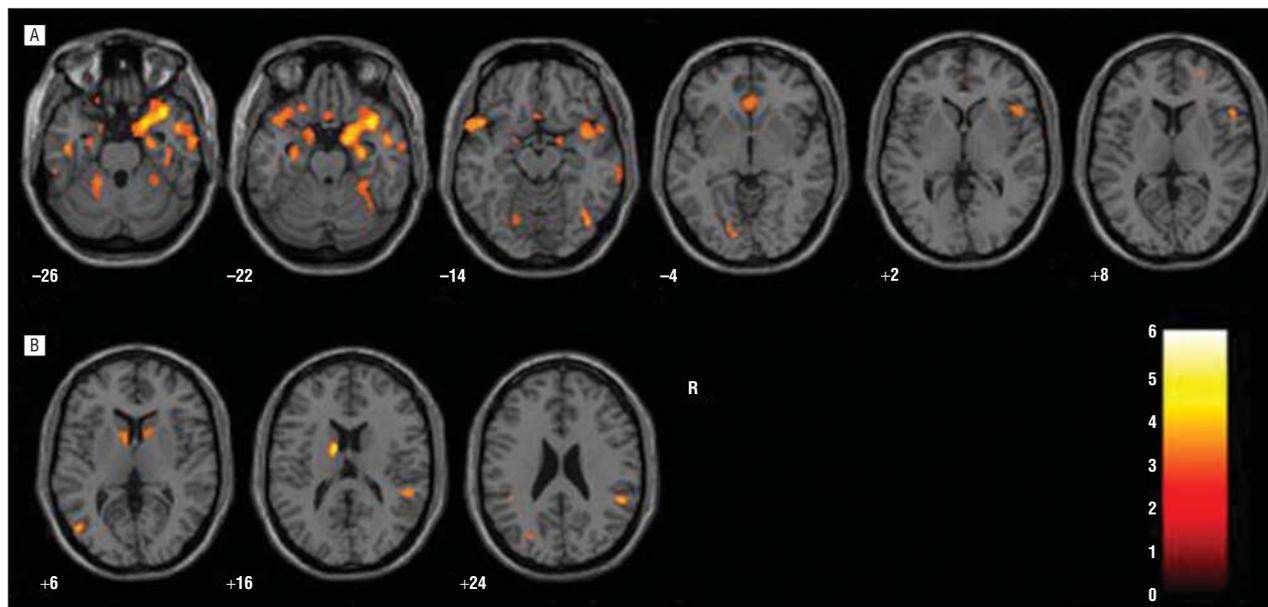


Figure 3. Decreases in gray matter associated with exposure to childhood maltreatment in girls and boys. T1-weighted axial-oblique views show regions where gray matter volume was inversely correlated with Childhood Trauma Questionnaire total scores (uncorrected $P < .005$ and cluster size of ≥ 50 voxels) in girls (A) and boys (B). The color bar shows t statistics and the numbers in white in the lower left corner of each image show the Montreal Neurological Institute z-plane coordinates (in millimeters).

pulsive, anxious, and depressive behaviors.^{49,55-57} The effects sustained during adolescence have been postulated to result from secondary dendritic spine remodeling and alterations in neurodevelopmental trajectories.^{2,58}

Associations between self-reported CM and volume reductions in RPF and DLPFC were prominent findings in this study. The prefrontal cortex is one of the brain regions that is most vulnerable to stress in animal models, showing stress-related decreases in dendritic length, branching, and spine densities.^{3,48,50,59} The RPF is associated with behavioral control functions, including attention direction, decision making, response inhibition, and emotion regulation.⁶⁰⁻⁶³ Bilateral DLPFC functions overlap RPF functions and also include working memory, cognitive reappraisal of affective experience, and behavioral planning.⁶⁴⁻⁶⁸ Reductions in these PFC regions (coupled with our findings in striatum, with which PFC shares strong connections⁶⁹) suggest that CM is associated with morphologic alterations in a neural system that subserves behavioral, cognitive, and emotional control functions that are frequently disrupted in those reporting CM.⁷⁰

Reports of physical abuse were also associated with reductions in insula. The insula is central to interoceptive functions that monitor bodily and emotional states and has been implicated in the experience of bodily ownership and agency, as well as empathic perception of emotional states in others.⁷¹⁻⁷⁵ We speculate that the association observed between physical abuse and the insula could contribute to alterations in perceptions of bodily ownership and personal agency, as well as dissociative symptoms observed in persons who have been exposed to childhood physical abuse.⁷⁶⁻⁷⁸

Volume decreases in sensory association regions, including temporoparietal and occipital areas, were noted across analyses. Consistent with studies showing altera-

tions in emotional face perception in adults,⁷⁹ adolescents,⁸⁰ and children^{81,82} exposed to CM, we found decreases in the fusiform gyrus, a region associated with face perception.⁸³ Our results in parietal association regions are notable given the association of attentional biases in perception with CM history in adults and children.^{84,85} Findings in these sensory association regions are consistent with parietal alterations observed in adults reporting CM exposure and borderline personality disorder⁸⁶ and parietal and occipital alterations in PTSD,⁸⁷ suggesting that CM may alter perceptual integration through adulthood via GM changes.

Reported physical neglect and emotional neglect were associated with volume decreases in cerebellum. The cerebellum has reciprocal connections with other CM-associated regions, including PFC, amygdala, and hippocampus,^{88,89} and contains high concentrations of glucocorticoid receptors.⁹⁰ Rodent models of neglect suggest alterations in glucocorticoid receptor expression and cell degeneration in the cerebellum.⁹¹ Previous investigations show reductions in cerebellar volume in neglected children⁹² and in children with PTSD secondary to maltreatment.⁹³ Cerebellar response has been associated with traumatic reminders in PTSD⁹⁴ and with recollection of emotional autobiographic information and fear conditioning.⁹⁵ Further studies of cerebellum in affective and anxious symptoms associated with CM are warranted.

Emotional neglect was also associated with volume reductions in a neural system subserving emotion regulation, including OFC, sgPFC, striatum, amygdala, and hippocampus,^{96,97} in which abnormalities have been shown in persons with mood disorders.⁹⁸⁻¹⁰⁰ Our results are consistent with rodent models of postnatal neglect that show decreases in brain-derived neurotrophic factor and neurogenesis in these corticostriatal-limbic regions.^{47,52,57,101}

These findings suggest that early emotional neglect may alter the development of this emotion regulation system, conferring increased risk for the development of mood disorders.

Results of our preliminary analyses among female participants suggest that the association between CM and the neural system that subserves emotion regulation may be potent in female adolescents. Within this group, inverse associations were found between the CTQ total scores and GM volume in the RPF, OFC, sgPFC, insula, temporal cortex, amygdala, hippocampus, and cerebellum. Pubertal hormones have organizing effects on this system, the development of this system and its development has been shown to be sexually dimorphic.^{31,32,102} Animal models suggest that estrogen may mediate stress sensitivity in PFC¹⁰³ and in hippocampus.¹⁰⁴ In contrast, in males, there was a trend toward reductions in RPF, and reductions in caudate were significant; these regions are key components in the neural circuitry that underlies impulse control.^{69,70} The development of this circuitry is also sexually dimorphic.^{31,105} Estrogen has been demonstrated to have a neuroprotective effect in striatum, suggesting reduced vulnerability in this region among females.¹⁰⁶ We speculate that the different regional patterns of GM decreases associated with self-reported CM in females and males may mediate their different vulnerabilities to disorders of mood and impulse control in adolescence.^{22,35,39,107-109}

Limitations of this study include the small sample sizes, particularly for those reporting sexual abuse. Although results in emotion regulation regions in association with emotional maltreatment were consistent with our hypotheses, emotional neglect was the most frequently reported subtype of CM; findings observed only within this subgroup may have resulted from greater power to detect differences. Timing and duration of CM exposure may influence GM volume differences.¹¹⁰ The CTQ ratings are limited by the use of retrospective self-reports and do not assess ages at which maltreatment occurred, hindering exploration of possible differential effects of the timing of maltreatment on brain development. Because the regional distribution of volume decreases associated with CM are similar to those observed in individuals with psychiatric and behavioral difficulties, we interpreted the volume decreases to represent vulnerability factors. However, because the adolescents studied did not meet criteria for disorders in spite of adversity, it is also possible that the GM decreases reflect resiliency. Longitudinal studies could help clarify what interactions that may exist between CM and development and whether findings observed herein represent risk or resiliency factors.

We identified brain alterations in a sample of adolescents who did not meet criteria for psychiatric diagnoses, suggesting that in the absence of known psychiatric disorders CM may alter corticostriatal-limbic GM. The functions of these regions suggest that in adolescents exposed to CM such GM changes may contribute to a spectrum of behavioral difficulties, including alterations in self and interpersonal perceptions and in impulse, cognitive, and emotional control.^{27,111-113} Scores on the CTQ scale used to assess CM were rated by the adolescents themselves. Although there are alternate methods of determining CM histories, such as using reports by care-

givers or established case histories in the clinical and child welfare settings, self-reports have been previously shown to be reliable and may be sensitive to CM that may not reach clinical awareness.^{41,42,114,115} Moreover, it has been theorized that an individual's perception of neglect or maltreatment may be especially relevant in the psychological and neuropsychological development of the child.¹¹⁶

Adolescence is a particularly vulnerable time for the development of mood, anxiety, and addictive disorders, and CM has been linked to increased vulnerability to these disorders.^{25,70,117-119} Findings herein suggest that corticostriatal-limbic brain changes may mediate increased risk for these disorders in association with self-reported CM. Together, these results highlight the critical need for improved understanding of effects of childhood abuse and neglect in adolescents and of possible differences in the effects of different CM subtypes on brain development. Although adolescents with a history of CM may have symptoms and behaviors that may not yet meet criteria for psychiatric diagnoses, detection and early intervention may help improve functioning and reduce risk for the development of mood, addictive, and other psychiatric disorders.

Accepted for Publication: April 20, 2011.

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Author Contributions: Dr Blumberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Edmiston, Guiney, Sinha, Mayes, and Blumberg. *Acquisition of data:* Sinha, Mayes, and Blumberg. *Analysis and interpretation of data:* Edmiston, Wang, Mazure, and Blumberg. *Drafting of the manuscript:* Edmiston, Mayes, and Blumberg. *Critical revision of the manuscript for important intellectual content:* Wang, Mazure, Guiney, Sinha, and Blumberg. *Statistical analysis:* Wang, Sinha, and Blumberg. *Obtained funding:* Wang, Mazure, Sinha, Mayes, and Blumberg. *Administrative, technical, and material support:* Wang, Mazure, Guiney, Sinha, Mayes, and Blumberg. *Study supervision:* Wang and Blumberg.

Financial Disclosure: None reported.

Funding/Support: This work was funded by grants K01MH086621 (Dr Wang) and R01MH69747 and R01MH070902 (Dr Blumberg) from the National Institute of Mental Health, by grant UL1-DE19586 from the National Institutes of Health Roadmap for Medical Research Common Fund (Dr Sinha), and by grants PL1-DA24859 (Dr Sinha), RL1DA024856 (Drs Mayes and Blumberg), RL5DA024858 (Dr Mazure), and K05DA020091 (Dr Mayes) from the National Institute of Drug Abuse. The study was also supported by the National Alliance for Research in Schizophrenia and Depression (Drs Wang and Blumberg), Klingenstein Foundation (Dr Wang), Women's Health Research at Yale (Drs Mazure and Blumberg), and Attias Family Foundation (Dr Blumberg).

Role of the Sponsors: The funding organizations had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Additional Contributions: Susan Quatrano, Philip Markovich, Kathryn Armstrong, Sarah Nicholls, Matthew Freiburger, and Matthew Hirschtritt assisted with the research participants, and Cheryl Lacadie, Karen Martin, Terry Hickey, and Hedy Sarofin provided technical expertise. We thank the research participants for taking part in the study.

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