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Arch Pediatr Adolesc Med. Author manuscript; available in PMC 2013 March 25.

Published in final edited form as:
Arch Pediatr Adolesc Med. 2011 December ; 165(12): 1069–1077. doi:10.1001/archpediatrics.2011.565.

Corticostriatal-limbic Gray Matter Morphology in Adolescents with Self-Reported Exposure to Childhood Maltreatment

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Abstract

Objective—To study the relationship between self-reported childhood maltreatment and cerebral gray matter in adolescents without psychiatric diagnoses.

Design—Associations between childhood maltreatment (measured by a childhood trauma self-report questionnaire for physical, emotional and sexual abuse, and physical and emotional neglect) and regional gray matter were examined.

Setting—University hospital.

Participants—42 adolescents without psychiatric disorders.

Outcome Measures—Correlations between childhood trauma questionnaire scores and regional gray matter volume were assessed in voxel-based analyses of structural magnetic resonance scans. Relationships between gray matter volume and childhood maltreatment subtypes and gender where explored.

Results—Total childhood trauma questionnaire scores correlated negatively ($p<0.005$) with gray matter volumes in prefrontal cortex, striatum, amygdala, sensory association cortices and cerebellum. Physical abuse, physical neglect and emotional neglect were associated with rostral prefrontal reductions. Additionally, decreases in dorsolateral and orbitofrontal cortices, insula, and ventral striatum were associated with physical abuse, in cerebellum with physical neglect, and in dorsolateral, orbitofrontal and subgenual prefrontal cortices, striatum, amygdala, hippocampus and cerebellum with emotional neglect. These latter emotion regulation regions were also associated with childhood trauma questionnaire scores in females, while caudate reductions, which may relate to impulse dyscontrol, were seen in males.

Conclusions—Childhood maltreatment was associated with corticostriatal-limbic gray matter reductions in adolescents. These findings suggest that even if adolescents reporting childhood maltreatment exposure do not present with symptoms that meet full criteria for psychiatric disorders, they may have corticostriatal-limbic changes that place them at risk for behavioral difficulties. Vulnerabilities may be moderated by gender and maltreatment subtype.

INTRODUCTION

An estimated 3.7 million children are assessed for child maltreatment (CM) each year in the United States; this number likely underestimates the number of children experiencing maltreatment since many do not come to professional attention.[1] Increasing evidence suggests these children may endure long-lasting neural consequences of CM that place them

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at risk for behavioral and psychiatric sequelae. Converging evidence supports adverse effects of early life stress on morphological development of corticostriatal-limbic structures.[2–4] Magnetic resonance imaging (MRI) studies show decreased corticostriatal-limbic gray matter (GM) volume in children and adults reporting exposure to CM.[5–14] GM changes in the intervening adolescent epoch can also be inferred. However, few studies focus on the neurobiological effects of CM in adolescents.

Corticostriatal-limbic GM volume decreases are well established in adults reporting CM. The hippocampus has been the region most studied in adults reporting exposure to CM, consistently demonstrating volume decreases.[5,8,9,10,13,15] Volume reductions in the prefrontal cortex (PFC), striatum and amygdala have also been demonstrated in studies of adults reporting CM.[8–12, 16] Furthermore, preclinical CM models implicate more widespread corticostriatal-limbic involvement,[3,16,17] suggesting a whole brain approach may be especially helpful in revealing distributed CM effects. Neuroimaging studies of CM have largely assessed adults with psychiatric disorders, especially post-traumatic stress disorder (PTSD) and borderline personality disorder, limiting ability to ascertain whether brain changes are related to CM and/or the disorders. These studies also often focused on CM broadly, limiting ability to determine effects of CM subtypes.

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

Associations between CM and GM volume in adolescents are inferred, but few studies focus on adolescents. Adolescents have been included in some pediatric studies, though often analyzed together with prepubertal children. One recent study of adolescents reporting more general early-life adversities, ranging from physical neglect and emotional abuse to witnessing domestic violence or experiencing a life threatening injury, did show hippocampus volume decreases.[20] This suggests that some differences found in adults, such as those in hippocampus, may be expressed by adolescence. To the best of our knowledge, there has not been a prior study that focused on adolescents reporting CM that used a whole brain approach to study distributed brain effects.

Similarities and differences in the sequelae of different types of abuse and neglect are not known, but could indicate differing vulnerabilities and need for differing detection and intervention approaches.[21] Although physical and sexual abuse have been associated with increased depression risk,[22,23] studies increasingly suggest emotional maltreatment may have strong effects on 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 emotional neglect may have long-lasting effects on corticostriatal-limbic regions subserving emotional regulation. Sex difference may also modify effects of CM on corticostriatal-limbic morphology. The sexually dimorphic development of stress-sensitive corticostriatal-limbic regions[30–33] have been suggested to contribute to sex differences in psychiatric disorders, such as in regions subserving emotions and increased depression risk in females and regions subserving impulse control and increased risk for substance abuse in males.[34–39]

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In this morphometric structural MRI 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 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 maltreatment subtypes would be associated with varying regional patterns of GM reductions, with emotional maltreatment associated with reductions in corticostriatal-limbic regions subserving emotional regulation. We also performed exploratory analyses by gender. We anticipated that GM volume reductions in corticostriatal-limbic brain regions subserving emotional regulation would be associated with CM exposure in females, while GM volume reductions in regions subserving impulse control would be associated with CM in males.

METHODS

Participants included 42 adolescents (ages 12–17years, mean 15.33±1.37years, 50% female, 19 Caucasian, 19 African American, 4 more than one race) without DSM-IV 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/guardians.[40] Subjects were recruited from a sample of children identified at birth to be at high risk for CM and followed longitudinally (by LCM). Participants were also recruited from the greater New Haven Connecticut community, allowing for a sample of adolescents reporting a spectrum of CM severity. Subjects were without history of neurological illness, head trauma with loss of consciousness or major medical disorder. Written informed consent was obtained from parents/guardians, and assent from minors, in accordance with the institutional review board of the Yale School of Medicine.

Children completed the Childhood Trauma Questionnaire (CTQ),[41,42] a self-report questionnaire on experience of five 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 (e.g., “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 a child's basic physical needs including food, shelter, safety, supervision and health (e.g. “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 any humiliating, demeaning, or threatening behavior directed toward a child by an older person (e.g., “People in my family said hurtful or insulting things to me”). *Emotional neglect* is defined as the failure of caretakers to provide basic psychological and emotional needs, such as love, encouragement, belonging and support (e.g. “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 (e.g. “Someone tried to make me do sexual things or try sexual things”). Participants rate items on the CTQ using a 5-point scale ranging from “never true” to “very often true.” Each CTQ subscale has five items so that subscale scores range from five (no maltreatment) to twenty-five (severe maltreatment). The five CM subtypes scores are summed for a Total CTQ score. All but six participants reported some form of CM, defined as a score of five or more on any of the five CM subtype scores. Physical abuse was reported by sixteen subjects, physical neglect by eighteen, emotional abuse by twenty-three, emotional neglect by thirty-four, and sexual abuse by six.

T-tests were performed to examine possible gender differences in age, CTQ total and subscale scores using Statistical Package for the Social Sciences for Windows, Version 11.1.[43]

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High-resolution structural MRI scans were obtained on a 3T Trio Scanner (Siemens, Erlangen, Germany) using a three-dimensional Magnetization Prepared Rapid Acquisition Gradient Echo T1-weighted sequence (TR=1500ms, TE=2.83ms, FOV=256 × 256 mm^2, matrix=256 × 256, 1.0mm sagittal slices without gap, 160 slices, NEX=2). Images were processed with the Statistical and Parametric Mapping 5 (SPM5) (http://www.fil.ion.ucl.ac.uk/spm) using our previous protocol.[44] Briefly, the SPM5 segmentation function was implemented 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 SPM5, covarying for age, to investigate the relationship between total CTQ scores and GM volume. Additional regression analyses of CTQ subscales and GM volume were performed only for subjects who reported the maltreatment subtype. Separate, exploratory regressions of CTQ total scores were also performed for female participants and for male participants. Results were considered significant at $p<0.005$ (uncorrected) and clusters >50voxels.

RESULTS

Females and males did not differ significantly in age, CTQ total or CTQ subscale scores. Total CTQ scores showed a significant inverse correlation with GM volume in bilateral dorsolateral prefrontal cortex (DLPFC) [Brodmann's Area (BA) 46/9], bilateral rostral prefrontal cortex (RPFC) (BA10), left subgenual PFC (sgPFC) (BA25), bilateral striatum and right amygdala, as well as left parietal (BA40/7) and right temporoparietal (BA22/40) association cortices, bilateral temporal cortex (BA20/21), right fusiform gyrus (BA20/37), bilateral occipital association cortex (BA18/19), bilateral cerebellum, and regions of hypothalamus and midbrain (Figure 1).

CTQ subscales scores showed inverse associations with GM volumes for self-reported: *physical abuse* with left DLPFC (BA46/9), left RPFC (BA10), right orbitofrontal cortex (OFC) (BA47), and right ventral striatum, right insula and right temporal association cortex (BA20/21) (Figure 2a), *physical neglect* with left RPFC (BA10), right parietal association cortex (BA40/39) and bilateral cerebellum (Figure 2b), *emotional neglect* with bilateral DLPFC (BA46/9), bilateral RPFC (BA10), bilateral dorsal anterior cingulate cortex (BA24/32), right superior frontal gyrus (BA8), right OFC (BA47), bilateral sgPFC (BA25), bilateral striatum, bilateral amygdala and hippocampus, left parietal association cortex (BA40), right temporal association cortex (BA20/38), left occipital association cortex (BA18/19), bilateral cerebellum, and regions of the midbrain and hypothalamus (Figure 2c). No significant results were found for emotional and sexual abuse subscales.

In females, CTQ total scores were inversely correlated with volume in right RPFC (BA10), bilateral OFC (BA11/47), bilateral sgPFC (BA25/32), bilateral amygdala and hippocampus, right insula, bilateral temporal association cortex (BA20/21/38), bilateral fusiform gyrus (BA20), right temporo-occipital association cortex (BA37/19), left occipital association cortex (BA18/19), and bilateral cerebellum (Figure 3a). In males, CTQ total scores were inversely correlated with volume in bilateral caudate, bilateral temporoparietal cortex (BA37/40) and left temporo-occipital association cortex (BA37/19) (Figure 3b). There was a trend towards an inverse association with left RPFC (BA10); the cluster size was beneath the study threshold at 44 voxels.

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COMMENT

Our results indicate that self-reported CM is associated with reductions in GM volume in a distributed corticostriatal-limbic system, including the DLPFC, RPFC, sgPFC, striatum, amygdala and hippocampus, as well as parietal, temporal and occipital association cortices and cerebellum. These findings were present in a sample of adolescents without psychiatric disorders. Results of exploratory analyses, while preliminary, support prominent reductions in RPFC volume common across physical abuse, physical neglect and emotional neglect CM subtypes, as well as patterns of additional regional volume decreases in the CM subtypes. Findings in females were in regions associated with emotional regulation, whereas in males with regions subserving impulse control.

Rodent and non-human primate models of CM show morphological alterations in PFC, striatum, amygdala and hippocampus.[45–54] The mechanisms that underlie these changes are not clear; acute effects of stress on corticostriatal-limbic morphology demonstrated in the basic models include epigenetic effects on the hypothalamic-pituitary-adrenal (HPA) axis, dysregulated functioning of neurotransmitter and intracellular signaling pathways, as well as reductions in neurotrophic factors and neurogenesis.[3,50–54] These morphological changes are associated with behavioral changes, including increased impulsive, anxious and depressive behaviors.[49,55–57] Effects sustained through 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 RPFC and DLPFC were prominent findings in this study. The PFC is one of the brain regions most vulnerable to stress in animal models, showing stress-related decreases in dendritic length, branching and spine densities.[3, 48,50.59] The RPFC is associated with behavioral control functions including directing attention, decision-making, response inhibition and emotional regulation.[60–63] DLPFC functions overlap RPFC functions, and 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 the PFC shares strong connections,[69] suggest CM is associated with morphological 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 the 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 these 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 alterations 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 of interest given the association of attentional biases in perception with CM history in both adults and children.[84,85] Findings in these sensory association regions are consistent with parietal alterations found in adults reporting CM exposure and borderline personality disorder[86] and parietal and occipital alterations in PTSD,[87] suggesting CM may alter perceptual integration through adulthood via GM changes.

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Reported physical 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 reports show reductions in cerebellar volume in neglected children[92] and children with PTSD secondary to maltreatment.[93] Cerebellar response has been associated with traumatic reminders in PTSD,[94] recollection of emotional autobiographical information and fear conditioning.[95] Together, these findings suggest further studies of the cerebellum in affective and anxious symptoms associated with CM are warranted.

Emotional neglect was additionally associated with volume reductions in a neural system subserving emotional regulation, including OFC, sgPFC, striatum, amygdala and hippocampus,[96,97] in which abnormalities have been shown in mood disorders.[98–100] Our findings 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 emotional regulation system, conferring increased risk for the development of mood disorders.

Our preliminary analyses within the female group suggest the association between CM and the neural system that subserves emotional regulation may be potent in female adolescents. Within this group, inverse associations were found between total CTQ scores and GM volume in the RPFC, OFC, sgPFC, insula, temporal cortex, amygdala, hippocampus and cerebellum. Pubertal hormones have organizing effects on 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 PFC[103] and hippocampus.[104] In contrast, in males, there was a trend towards reductions in RPFC and reductions were significant in caudate; these regions are key components in the neural circuitry that underlies impulse control.[69,70] Development of this circuitry is also sexually dimorphic;[31,105] estrogen has been demonstrated to have a neuroprotective effect in the striatum, suggesting reduced vulnerability in this region in females.[106] We speculate that the different regional patterns of gray matter 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 small sample sizes, particularly for those reporting sexual abuse. While findings in emotional regulation regions in association with emotional maltreatment were consistent with hypotheses, emotional neglect was the most frequently reported subtype; findings seen only within this subgroup may have resulted from greater power to detect differences. Timing and duration of CM exposure may influence GM differences.[110] CTQ ratings are limited by the use of retrospective self-reports and do not assess ages at which maltreatment occurred, making exploration of possible differential effects of the timing of maltreatment on brain development difficult. As the regional distribution of the volume decreases with CM are similar to those found in psychiatric and behavioral difficulties, we interpreted the volume decreases to represent vulnerability factors. However, especially as the adolescents studied did not meet criteria for disorders despite adversity, it is also possible that the gray matter decreases reflect resiliency. Longitudinal studies could help clarify interaction of CM and development, and whether findings observed 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 GM changes may contribute to a spectrum of behavioral difficulties experienced by adolescents exposed to CM, including alterations in self and interpersonal perceptions, as well as in impulse, cognitive and emotional control.[27,111–113] The CTQ scale used to assess CM was rated by the adolescents themselves. Though there are alternate methods of determining CM histories, such as reports by caregivers and/or established in the clinical and child welfare settings, self-reports have been shown previously 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 the neglect and/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.[25,69,117–119] This study suggests that corticostriatal-limbic brain changes may mediate increased risk for these disorders in association with self-reported CM. Together, these findings highlight the critical need for improved understanding of effects of both childhood abuse and neglect in adolescents and possible differences in their effects on brain development. Though adolescents with CM history may have symptoms and behaviors that may not yet reach full criteria for psychiatric diagnoses, detection and early intervention may help to improve functioning and reduce risk for the development of mood, addictive and other psychiatric disorders.

Acknowledgments

This work was supported by grants from the National Institute of Mental Health R01MH69747 (HPB), R01MH070902 (HPB), K01MH086621 (FW), National Institute of Health (NIH) Roadmap for Medical Research Common Fund grant UL1-DE19586 (RS) and NIH Roadmap for Medical Research/Common Fund (RS), National Institute of Drug Abuse RL1DA024856 (HPB, LCM), K05DA020091 (LCM) and PL1-DA24859 (RS), Women's Health Research at Yale (HPB, CMM), National Alliance for Research in Schizophrenia and Depression (HPB, FW), Attias Family Foundation (HPB), and Klingenstein Foundation (FW). The funding organizations did not have roles in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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

We thank Susan Quatrano, Philip Markovich, Kathryn Armstrong, Sarah Nicholls, Matthew Freiburger, and Matthew Hirschtritt for their efforts with the research subjects, Cheryl Lacadie, Karen Martin, Terry Hickey and Hedy Sarofin for technical expertise, and the research subjects for their participation.

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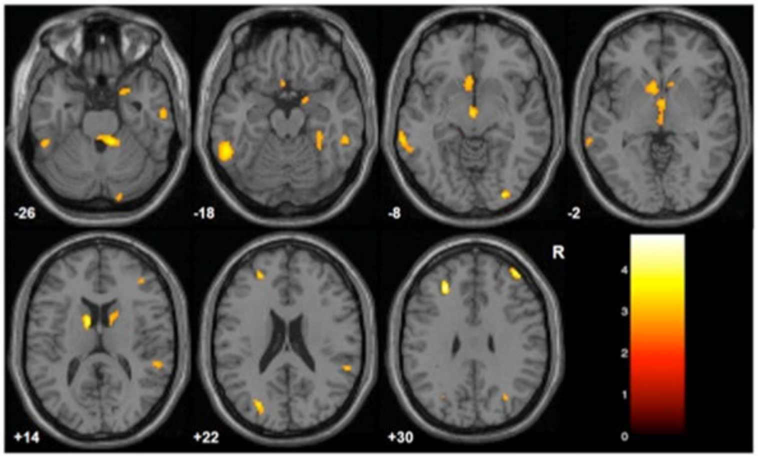

Figure 1. Gray Matter Decreases Associated with Childhood Maltreatment

The images display regions where gray matter volume was inversely correlated with Childhood Trauma Questionnaire total scores, $p<0.005$ (uncorrected), cluster ≥50voxels. The color bar displays T-values, Montreal Neurological Institute z-plane coordinates (millimeters); R=right.

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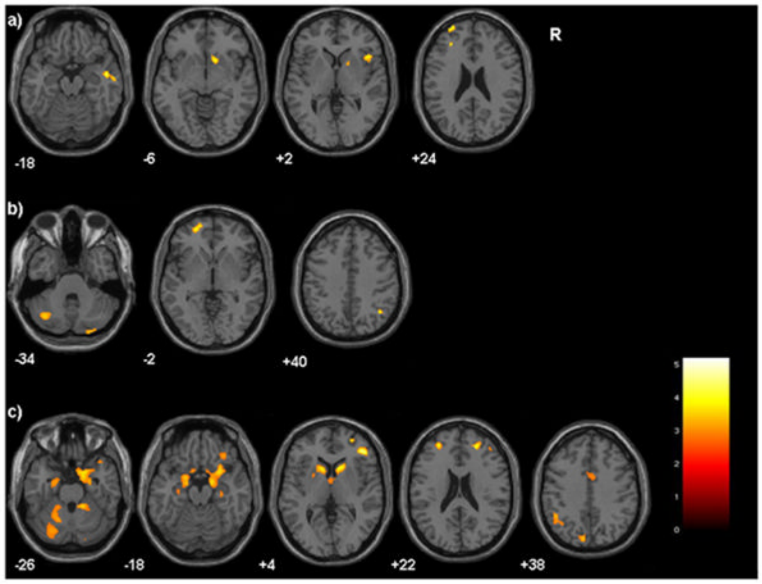

Figure 2. Gray Matter Decreases Associated with Childhood Maltreatment Subtypes
Axial-oblique images display regions where gray matter volume was inversely correlated with Childhood Trauma Questionnaire subscale scores, $p<0.005$(uncorrected), cluster ≥50voxels for: a)physical abuse b)physical neglect c)emotional neglect. The color bar displays T-values, Montreal Neurological Institute z-plane coordinates (millimeters); R=right.

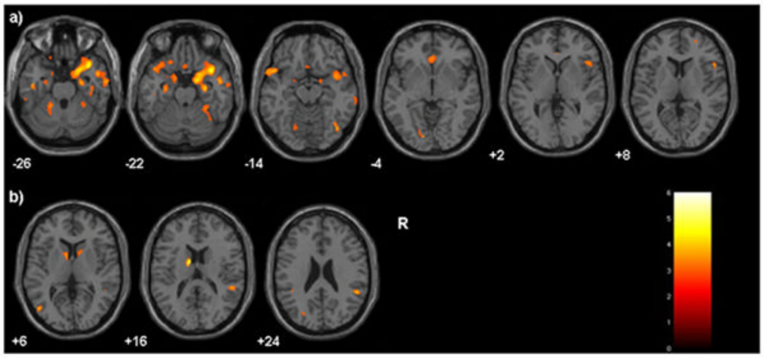

Figure 3. Gray Matter Decreases Associated with Childhood Maltreatment in Females and Males

T1 axial-oblique images display regions where gray matter volume was inversely correlated with Childhood Trauma Questionnaire scores in a) females and b) males, $p<0.005$ (uncorrected), cluster≥50. The color bar displays T-values, Montreal Neurological Institute z-plane coordinates (millimeters); R=right.

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