

Childhood Sexual Abuse Is Associated with Reduced Gray Matter Volume in Visual Cortex of Young Women

Akemi Tomoda, Carryl P. Navalta, Ann Polcari, Norihiro Sadato, and Martin H. Teicher

Background: Childhood sexual abuse (CSA) has been associated with alterations in brain morphology using region of interest analyses that have focused on stress-sensitive target regions. This study was designed to ascertain the effects on gray matter volume (GMV) of exposure to CSA in healthy young adult college students selected based on exposure history regardless of psychiatric outcome. Voxel-based morphometry (VBM) provided unbiased delineation of the most significantly affected brain regions.

Methods: High-resolution T1-weighted magnetic resonance imaging (MRI) datasets were obtained for 23 unmedicated female subjects with CSA and 14 healthy female control subjects of equivalent age and socioeconomic status with no history of trauma. Cortical surface-based analysis (FreeSurfer) was performed to verify VBM results.

Results: Gray matter volume was reduced by 12.6% and 18.1% in right and left primary visual (V1) and visual association cortices of abused subjects. This reduction was directly related to duration of CSA before age 12. Gray matter volume of left and right V1 correlated with measure of visual memory ($r = .353, p = .032$ and $r = .448, p = .005$). Cortical surface-based analysis indicated that GMV of abused subjects was reduced in the left fusiform ($p = .004$), left middle occipital ($p = .04$), and right lingual ($p = .002$) gyri.

Conclusions: Early visual experience exerts a strong influence on the developing mammalian visual cortex. Present findings indicate that exposure to CSA may also affect the development of this region and are apparent even in a population of subjects who are sufficiently healthy to matriculate.

Key Words: Childhood sexual abuse (CSA), gray matter volume (GMV), sensitive period, visual cortex, voxel-based morphometry (VBM)

Exposure to abuse or neglect is common throughout the world and is a major risk factor for psychopathology (1). Childhood abuse has been associated with volume loss in the hippocampus (2–5), corpus callosum (6,7), and prefrontal cortex (8), with altered symmetry in frontal lobes (9) and superior temporal gyrus (10) and with reduced neuronal density or integrity in the anterior cingulate (11). We have proposed that brain regions may be modified by exposure to adversity as a consequence of a cascade of events that include excessive exposure to stress hormones (cortisol, norepinephrine, vasopressin) and overactivation of monoamine neurotransmitter systems (12), particularly if the exposure occurs during a sensitive developmental period (13).

Research in this area has the potential to recast our thinking about the role of early experience in psychopathology (12,14), but current studies are limited by their reliance on clinical samples consisting of abused subjects with a specific form of psychopathology, such as posttraumatic stress disorder (PTSD). Consequently, these studies may 1) overestimate the effects of abuse by selecting the most adversely affected subjects, 2) confound abuse-related differences with disorder-related differences, or (3) mistakenly

identify preexisting brain abnormalities that were risk factors for developing a specific disorder when exposed to trauma rather than regions altered by the exposure (15). This latter point is not necessarily a concern if the focus of the study is the neurobiology of a particular disorder, but it is a problem if the focus is on the neurobiological consequences of abuse. Furthermore, current studies use region of interest (ROI) analyses and predominantly focus on target structures presumed to be vulnerable. This approach is valuable and typically hypothesis-driven, but it may hinder discovery of unanticipated outcomes.

The aim of this study was to use voxel-based morphometry (VBM) as an unbiased, whole brain approach to identify alterations in regional gray matter volume (GMV) in individuals recruited from the community with exposure to childhood sexual abuse (CSA), but no other forms of trauma, and enrolled regardless of psychiatric outcome.

Methods and Materials

Subjects were right-handed, healthy, unmedicated young adults (18–22 years of age) with excellent hearing and visual acuity, recruited by advertisements targeted to college students, and selected based on a complete absence of exposure to trauma or a self-reported history of forced contact CSA. This narrow age range was chosen to recruit subjects as close to the experience as possible who could provide independent informed consent and to minimize variations in brain morphometry related to development or aging. The McLean Hospital Institutional Review Board approved all procedures. The purpose and meaning of the study were explained to subjects, who subsequently gave their written informed consent.

This was a two-phase study. During the first phase, a large number of subjects interested in participating in the second (neuroimaging) phase provided detailed information on their degree of exposure to a host of abusive or traumatic experiences, along with medical, psychiatric, developmental, and family history. Applicants were aware that the neuroimaging study was on the effects of early experience on brain development but un-

From the Department of Psychiatry (AT, CPN, MHT), Harvard Medical School, Boston, Massachusetts; Developmental Biopsychiatry Research Program (AT, CPN, AP, MHT), McLean Hospital, Belmont, Massachusetts; Department of Child Developmental Sociology (AT), Faculty of Medical and Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan; and National Institute for Physiological Sciences (NS), Okazaki, Aichi, Japan.

Address correspondence to Akemi Tomoda, M.D., Ph.D., Developmental Biopsychiatry Research Program, McLean Hospital, 115 Mill Street, Belmont, MA 02478-9106; E-mail: tomo@kumamoto-u.ac.jp.

Received Dec 13, 2008; revised Mar 28, 2009; accepted Apr 3, 2009.

aware of our specific emphasis on CSA, so no candidate could fake or embellish a history to gain entry. Subjects were excluded who had any history of serious motor vehicle accident, near drowning, gang violence, muggings, natural disasters, or other forms of trauma; substance abuse; any recent substance use; head trauma with loss of consciousness; significant fetal exposure to alcohol or drugs; perinatal or neonatal complications; neurological disorders; or medical conditions that could adversely affect growth and development.

History of exposure to CSA was obtained in two ways. Individuals with CSA were initially identified if they responded affirmatively to the question: "Have you ever been forced into doing more sexually than you wanted to do or were too young to understand? (By 'sexually' we mean being forced against your will into contact with a sexual part of your body or of his/her body)." They also provided information on their relationship with this individual, number of times they were forced, age of first and last abuse, and whether or not they felt terrified or had their life or another person's life threatened (16).

Respondents meeting eligibility requirements were further evaluated using the Traumatic Antecedents Interview (TAI) (17). This is a 100-item, semistructured interview designed to evaluate reports of physical abuse (PA) or sexual abuse, witnessing violence, physical or emotional neglect, significant separations or losses, verbal abuse, or parental discord (17). The reliability of TAI variables ranges from acceptable to excellent (median intraclass $R = .73$) (17). Subjects needed to be consistent on both self-report and interview.

We selected subjects who reported three or more episodes of forced contact CSA accompanied by fear or terror, occurring before age 18 and at least 2 years before enrollment. Multiple episodes were required based on the assumption that CSA is typically a repeated event and that persistent fear of recurrence may be a major factor affecting brain development.

Licensed psychiatric clinical nurse specialists conducted the assessment interviews and completed their evaluations before neuroimaging. Interviews included the Structured Clinical Interview for DSM-IV for Axis I Disorders (18), Revised Diagnostic Interview for Borderlines (19), Structured Clinical Interview for DSM-IV Dissociative Disorders (20), and DSM-IV attention-deficit/hyperactivity disorder (ADHD) items taken from the Schedule for Affective Disorders and Schizophrenia for School-Aged Chil-

dren-Epidemiologic Version (K-SADS-E) (21). A panel of three doctoral level psychiatric clinicians with extensive experience treating traumatic disorders who were blind to the neuroimaging results reviewed questions regarding eligibility. Decisions were made by full consensus.

We also administered the Memory Assessment Scales (MAS) (22), which measure short-term, visual, verbal, and global memory. Subjects completed a Go/No-Go/Stop continuous performance task (CPT) (23) to assess components of attention, including visual discrimination and response inhibition.

The initial goal was to recruit 30 subjects with CSA and 30 control subjects with relatively equivalent gender ratios. Altogether, 723 individuals responded to advertisements and passed an initial phone screen regarding age, handedness, health, and medications. Of these, 554 completed detailed ratings that enabled us to identify potentially eligible subjects. Ten percent ($n = 53$) indicated a history of exposure to CSA unaccompanied by exposure to physical abuse, neglect, or witnessing domestic violence. Seventy-five percent indicated abuse by individuals outside their family. Screening for exposure to other forms of trauma and exclusionary medical history further reduced the sample. All CSA subjects meeting inclusion and exclusion criteria were invited to the laboratory for additional screening; 35 accepted. The selected neuroimaging pool included 16 female and 14 male control subjects and 26 female subjects and 4 male subjects with CSA. The disproportionate gender ratio in the CSA group was attributable to the lower incidence of CSA and high rate of exposure to other forms of abuse or trauma in male subjects. Because so few men were in the abused sample, we only analyzed female subjects. Altogether, artifact-free images suitable for VBM were available for 23 abused women and 14 female control subjects (Table 1).

Four subjects with CSA (17%) had current major depression, four had PTSD, and one (4%) had depersonalization disorder. No subjects met criteria for borderline personality disorder (BPD) or had a history of ADHD. Control subjects had no history of Axis I disorders. Abused and control subjects were predominantly middle class or higher (96%) and had similar measures of parental socioeconomic status (SES) (24) and cognitive abilities as evaluated using the MAS (22) and Scholastic Aptitude Test scores (Table 1). Self-reported onset of CSA was at 2 to 15 years of age, lasting for an average of 4.1 years (range 1–12). All CSA

Table 1. Demographic and Clinical Characteristics of Childhood Sexual Abuse Subjects and Control Subjects

Measures	Healthy Control Subjects	CSA Subjects	ANOVA	
			F Value	p Value
Subjects	14	23		
Age	19.0 ± 1.1	20.2 ± 1.3	7.59	.009
Socioeconomic Status	1.93 ± .73	2.26 ± .92	1.33	.26
Memory Assessment Scale Short-Term	110.5 ± 11.5	106.1 ± 11.0	1.36	.25
Memory Assessment Scale Verbal	109.1 ± 14.1	109.8 ± 12.7	.02	.88
Memory Assessment Scale Visual	114.2 ± 16.3	118.3 ± 8.7	.99	.33
Memory Assessment Scale Global	114.1 ± 14.2	117.1 ± 10.1	.56	.46
Scholastic Aptitude Test Math + Verbal	1299 ± 103	1255 ± 142	.93	.34
Limbic System Checklist-33	10.6 ± 6.1	29.0 ± 11.7	29.50	.00001
Dissociative Experience Scale	3.2 ± 3.4	15.6 ± 12.6	12.69	.001
Kellner SQ Anxiety	4.8 ± 3.9	11.6 ± 5.1	18.23	.0001
Kellner SQ Depression	4.1 ± 4.1	11.5 ± 6.3	15.10	.0004
Kellner SQ Somatization	3.7 ± 3.0	9.6 ± 6.7	9.53	.004
Kellner SQ Anger/Hostility	4.2 ± 3.0	8.0 ± 5.9	4.86	.03
Adult Suicidal Ideation Questionnaire	28.6 ± 14.2	60.8 ± 28.8	10.07	.004

ANOVA, analysis of variance; CSA, childhood sexual abuse; SQ, Symptom Questionnaire.

subjects had enduring memories of the abuse. None of the subjects had “recovered memories,” nor were any pursuing legal action against the abuser.

Magnetic resonant (MR) images were acquired on a General Electric Medical Systems 1.5-T Horizon LX Echo Speed scanner with a prototype Pathway MRI quadrature (General Electric, Milwaukee, Wisconsin), receive-only, volume head coil. The anatomical image series consisted of T1- and T2-weighted sagittals, T2-weighted axials, volumetric T1-weighted coronals, and anatomical dual-echo axials (proton and T2-weighted). Parameters for the volumetric T1-weighted coronal images were three-dimensional (3-D), Fourier transform (FT), spoiled gradient recalled acquisition (SPGR) pulse sequence (repetition time [TR] = 35, echo time [TE] = 5 msec/Fr; flip angle = 45 degrees, field of view [FOV] = 22 cm × 16 cm, 1.5 mm slice with no skip, 256 × 192 matrix, number of excitations (NEX) 1).

Voxel-based morphometry was performed using SPM5 (Statistical Parametric Mapping 5, developed by The Wellcome Department of Imaging Neuroscience, University College London, United Kingdom; <http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>) (25–28) running in MATLAB 6.5 (The MathWorks, Inc., Natick, Massachusetts). Images were segmented coarsely into gray matter, white matter, cerebrospinal fluid, and skull/scalp compartments using tissue probability maps. We used a standard template (Ashburner and Friston [25,29]), which conforms to the space defined by the International Consortium for Brain Mapping (ICBM), National Institutes of Health (NIH) P20 project. It approximates the space described in the Talairach and Tournoux atlas (30). The transform for this normalization was used to rewrite the original image into standard space. Volume changes induced by normalization were adjusted via a modulation algorithm. Spatially normalized images were segmented into gray and white matter and then smoothed using a 12-mm full-width half-maximum isotropic Gaussian kernel. Regional differences in GMV between groups were analyzed statistically using the general linear model. Potential confounding effects of SES and whole-segment GMV differences were modeled and variances attributable to them were excluded. The resulting set of voxel values used for comparison generated a statistical parametric map of *t* statistic (SPM{t}) that was transformed to a unit normal distribution (SPM{Z}). Statistical threshold was set at *p* < .05 with correction for multiple comparisons at cluster level (height threshold of *Z* > 3.09) because of the

increased sensitivity of clusters to detect spatially extended signal changes (31,32). Inference testing was based on the theory of Gaussian fields (33). We corrected for potential problems relating to nonisotropic smoothness, which can invalidate cluster level comparisons (25), by adjusting cluster size from the resel per voxel image (31,34). Exploratory correlation analyses between neuropsychiatric measures and regions of reduced GMV were performed to identify potential functional correlates, with correction for multiple comparisons.

Voxel-based morphometry is a potentially powerful technique for identifying morphometric differences, but it hinges on a number of assumptions, particularly the accuracy of image co-registration (35). Hence, VBM findings were reevaluated using an independent technique that does not rely on image co-registration. Cortical surface-based analysis was performed using the FreeSurfer program distributed by the Massachusetts General Hospital Nuclear Magnetic Resonance Center and CorTechs (Boston, Massachusetts) (36–38). Each subject's reconstructed brain was converted to an average spherical surface representation that optimally aligned sulcal and gyral features for the individual subject (36,37). Subdivision of the cortical ribbon into gyral-based subdivisions caused the identification of 82 validated cortical parcellation units per hemisphere. By application of the original deformation algorithms in reverse, ROIs were mapped back on to each unfolded surface (37,39). Differences between abused and control groups were assessed using analysis of covariance with SES and total brain volume as covariates. Parcellation regions selected for analysis were located in and around the areas of greatest difference identified by VBM. They included the lingual, fusiform, middle occipital, and inferior occipital gyri, plus the cuneus and occipital pole. A comprehensive report of FreeSurfer measures of thickness, surface area, and GMV across the myriad parcellation regions will be published separately.

Results

There were two significant clusters of reduced GMV in CSA subjects (Figure 1). The largest involved left primary (V1) and secondary (V2) visual cortex (Brodmann area [BA] 17/18; Talairach's coordinates *x* = −30 to −14, *y* = −89 to −70, *z* = −9 to 2) (*Z* = 4.03, corrected cluster level). A slightly smaller cluster was seen in the same regions on the right side (Talairach's

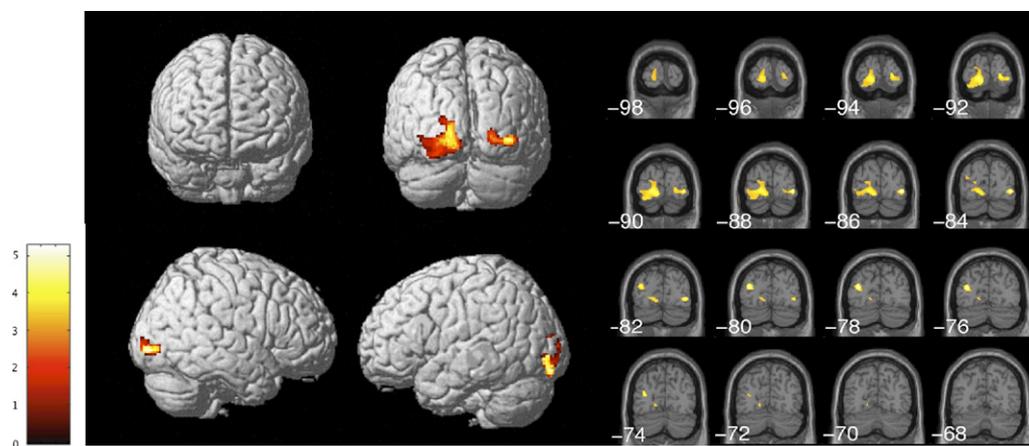


Figure 1. Portrayal of the locations of significant differences between abused subjects and control subjects in regional gray matter volume as revealed by voxel-based morphometry. Significantly lower gray matter densities in abused subjects were measured in the left and right visual cortex. Color scale: 0 to 5 represents *t* values.

coordinates $x = 16$ to 40 , $y = -89$ to -72 , $z = 1$ to 5) ($Z = 3.87$, corrected cluster level). Compared with healthy control subjects, there was an 18.1% and 12.6% average reduction of GMV in left and right visual cortex clusters of CSA subjects, respectively. Since the mammalian visual cortex appears susceptible to the effects of visual experience that occurs before puberty, data were analyzed to ascertain whether reduction in GMV in V1 was related to abuse before age 12 or at later ages. Multiple regression analysis, including duration of abuse before age 12 and from 12 years on and total GMV, indicated that GMV in left and right V1 correlated with the duration of CSA that occurred before age 12 ($\beta = -.362$, $p = .02$; $\beta = -.323$, $p < .03$). Primary visual cortex GMV did not significantly correlate with the duration of CSA from 12 years of age on ($\beta = -.303$, $p = .06$; $\beta = -.146$, $p > .3$). There was no significant correlation between age of onset of CSA and GMV in left or right V1 ($r = .242$, $p > .2$; $r = .099$, $p > .6$).

To ascertain whether the association between alterations in visual cortex GMV was a consequence of psychiatric illness, abused subjects who did not meet criteria for an Axis I psychiatric disorder ($n = 14$) were analyzed separately versus control subjects. A significant reduction in GMV of left BA 17 to 18 ($x = -26$ to -15 , $y = -89$, $z = -12$ to -3 ; $Z = 4.42$, uncorrected) was observed in abused subjects without Axis I psychopathology.

There were significant correlations between visual cortex GMV and measures of visual memory on the MAS. Left and right BA 17 to 18 GMV correlated with visual memory across all subjects, respectively ($r = .353$, $p = .032$; $x = -12$, $y = -73$, $z = 17$; $r = .448$, $p = .005$; $x = 12$, $y = -85$, $z = 17$). This relationship was quite apparent in healthy control subjects ($r = .629$, $p = .016$; $r = .778$, $p = .001$), but was not apparent in subjects with CSA ($r = .135$, $p > .5$; $r = .061$, $p > .7$). However, lack of correlation in CSA subjects may have been secondary to an anomalous data point (Figure 2). Excluding that point revealed a

significant correlation in CSA subjects ($r = .484$, $p = .022$) and parallel regression slopes across groups ($F = .456$, $df = 1,33$, $p > .5$). Gray matter volume in left V1 correlated marginally ($r = .361$, $p = .054$, $n = 29$) with the capacity to distinguish targets from nontargets on the Go/No-Go/Stop CPT, across all subjects tested.

No other areas of reduction were found with a corrected cluster probability value that approached significance. Examination of voxels with increased GMV in CSA subjects identified no significant corrected voxel-level cluster regions. There was one small region of increased GMV in CSA subjects in the left middle frontal gyrus (BA 8, $x = -38$, $y = 30$, $z = 50$, cluster size = 159) that was significant ($Z = 3.77$) at the uncorrected voxel level.

FreeSurfer results were highly complementary. As illustrated in Figure 3, the analysis revealed an 8.0% reduction in left visual cortex GMV ($F = 8.3$, $df = 1,34$, $p = .007$). This was specifically related to an 18.0% reduction in the left fusiform gyrus ($F = 9.5$, $df = 1,34$, $p = .004$) and a 9.5% reduction in the left middle occipital gyrus ($F = 4.5$, $df = 1,34$, $p = .041$). A 5% lower value was found for GMV for the entire right visual cortex ($F = 4.7$, $df = 1,34$, $p = .038$), which was attributable to an 8.9% reduction in the right lingual gyrus ($F = 11.2$, $df = 1,34$, $p = .002$). Gray matter volume in the left V1 cluster identified by VBM correlated significantly with GMV in left fusiform ($r = .441$, $p = .006$) and left middle occipital ($r = .452$, $p = .005$) gyri. Similarly, the right V1 cluster correlated strongly with GMV in right lingual gyrus ($r = .570$, $p < .001$).

Discussion

Gray matter volume was significantly reduced in left and right lingual (BA 17) and inferior occipital gyri (BA 18) of young adults with CSA. This unexpected finding emerged from a global VBM analytic approach. Cortical surface-based analyses confirmed a significantly lower GMV in the left > right visual cortex. Previous studies on the effects of early abuse focused on ROIs and did not report results for occipital cortex, with one notable exception. Fennema-Notestine *et al.* (40) conducted a volumetric magnetic resonance imaging (MRI) study of victims of intimate-partner violence (IPV). These individuals had significantly lower occipital GMV that was associated with exposure to childhood abuse rather than IPV. Together, these studies suggest that exposure to abuse affects visual cortex development but that vulnerability is limited to an early sensitive period.

We found that reduced right and left V1 GMV was significantly associated with duration of CSA before age 12 but not after. This age cutoff was selected for three reasons. First, Hubel and Wiesel (41) reported that the sensitive period for the effects of visual experience on the visual cortex of kittens extended until about 3 months of age, which is the earliest onset point for puberty in that species. Second, Lewis and Maurer (42) reported that human perceptual development remains vulnerable to damage from adverse visual experience until 10 to 13 years. Third, Garey (43) reported that synaptogenesis in V1 is rapid after birth with maximal synaptic density occurring at about 8 months. Thereafter, synapses are eliminated to reach "adult" levels at about 11 years. Hence, we hypothesized that the visual cortex should be relatively plastic through about 11 years of age, with menses beginning on average at about age 12. Unfortunately, we did not collect data on menarche, which may have provided a more meaningful demarcation point.

Why the visual cortex may be affected is an interesting question. We have proposed that exposure to different forms of abuse may have shared neurobiological consequences (related to their com-

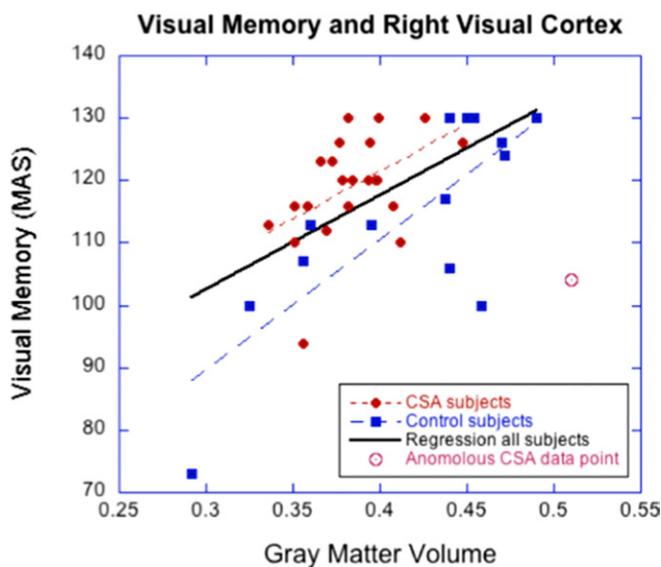


Figure 2. Scatter plot portraying the relation between gray matter volume and visual memory on the Memory Assessment Scale at the cluster location of maximal correlation in right lingual gyrus ($x = 12$, $y = -85$, $z = 17$). Linear regression for all subjects and for control subjects only, shown as solid black line and dashed blue line. Regression in CSA subjects (red dotted line) shown excluding anomalous data point ($r = .484$). There was no significant correlation between visual memory and right V1 GMV in CSA subjects with all points included ($r = .061$). CSA, childhood sexual abuse; GMV, gray matter volume; MAS, Memory Assessment Scales; V1, primary visual cortex.

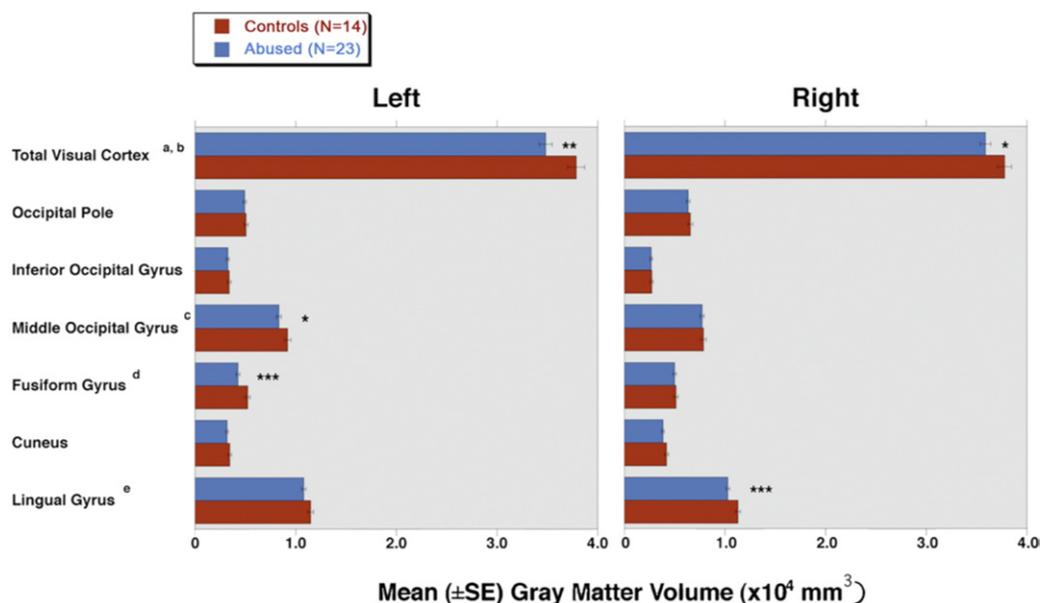


Figure 3. Mean (\pm SE) gray matter volume (GMV) in the visual cortex acquired by cortical surface-based analysis showing differences between healthy control subjects and subjects with repeated exposure to childhood sexual abuse. * $p < .05$; ** $p < .01$; and *** $p < .005$. ^aSignificant difference between two groups in the left visual cortex (abused $34,838 \pm 627$ vs. control subjects $37,886 \pm 838$; $F = 8.3$, $df = 1.34$, $p = .007$). ^bSignificant difference between two groups in the right visual cortex ($35,887 \pm 518$ vs. $37,773 \pm 693$; $F = 4.7$, $df = 1.34$, $p = .038$). ^cSignificant difference between two groups in the left middle occipital gyrus (8347 ± 243 vs. 9219 ± 325 ; $F = 4.5$, $df = 1.34$, $p = .041$). ^dSignificant difference between two groups in the left fusiform gyrus (4285 ± 181 vs. 5226 ± 242 ; $F = 9.5$, $df = 1.34$, $p = .004$). ^eSignificant difference between two groups in the right lingual gyrus ($10,289 \pm 179$ vs. $11,300 \pm 239$; $F = 11.2$, $df = 1.34$, $p = .002$).

mon action as stressors) and unique consequences related to sensory systems activated by the stress (44,45). Specifically, the child's brain may endeavor to reduce distress by attenuating the development of sensory systems and pathways relaying recurrent aversive or traumatic experiences (44). This may emerge as a form of experience-dependent plasticity that occurs during a sensitive period (13). Such periods allow experience to instruct neural circuits to process or represent information in ways that are adaptive for the individual (46). This is consonant with our hypothesis that abuse-associated neurobiological alterations may not simply reflect damage but may serve some adaptive purpose (47). The effect of experience on the brain during periods of high plasticity can alter axonal or dendritic morphologies, produce or eliminate synapses, and change the strength of synaptic connections (46). This hypothesis applies to other sensory systems as well. We recently reported that exposure to parental verbal abuse was associated with reduced fractional anisotropy in the left arcuate fasciculus, which connects Wernicke's and Broca's areas, and is important for verbal comprehension (45). Conversion disorders, including loss of vision or hearing, and dissociative disorders can also result from abuse (48,49), suggesting an array of potential mechanisms that may serve to protect the individual by reducing the biological or psychological impact of exposure.

Although we have discussed this finding in terms of a potential cause and effect mechanism, it must be emphasized that we only have evidence of an association. A possible alternative explanation for reduced occipital GMV is that children with ADHD may be at increased risk for CSA and that ADHD has been associated with altered occipital GMV. However, no subject in this sample had a history of ADHD. Moreover, the association between ADHD and exposure to CSA is modest and may apply only to the inattentive subtype (50). Another alternative explanation that we cannot reject is that reduced visual cortex GMV may be a preexisting abnormality that enhances risk of CSA. However, there is no other evidence to support this conjecture. Another unsupported

possibility is that reduced occipital GMV runs in families and is associated with increased likelihood of pedophilic or incestuous behaviors. Most subjects in this study experienced CSA from unrelated individuals. No subject in this sample reported CSA by biological parents. The predicted observation that V1 GMV correlated with the duration of abuse up to 11 years of age, but not after, is consistent with a causal relation.

FreeSurfer revealed that the most strongly affected components in this area were the left fusiform and right lingual gyri. The fusiform or occipitotemporal gyrus plays an important role in the recognition of faces (51), words (52), objects (53), and colors (54). Activity in the fusiform gyrus tends to be right lateralized for unfamiliar faces, bilateral for objects, and left lateralized for printed words (55). The right fusiform appears to be specialized for processing a face as a whole, and the left fusiform is apparently specialized for processing based on facial features (56). Moreover, the left fusiform gyrus was found to be activated specifically when viewing one's own face (57) and remembered faces (58). It is conceivable that reduced GMV in left but not right fusiform gyrus may bias facial perception and help explain the tendency of some patients to interpret ambiguous facial expressions as angry (59).

The right lingual gyrus appears to be involved in the global aspects of figure recognition (distinguishing a forest from trees) (60) and object naming (61). It may also be a critical substrate for dreaming (62) and is a brain region that consistently shows reduced cerebral blood flow after sleep deprivation or disruption (63,64). Nightmares and sleep disruption are frequently reported sequelae of CSA (65–69). Sleep disruption caused by CSA may diminish activity and blood flow to this region and consequently alter its developmental trajectory.

Overall, the association between exposure to CSA and reduced GMV in the visual cortex is particularly intriguing, given the historic importance of the visual cortex in elucidating the role of early experience on brain development (41). Furthermore, the obser-

vation of a potential sensitive period during which the visual cortex is maximally vulnerable to CSA argues for the value of early intervention or prevention strategies.

The main limitation of this study is the small sample size, particularly that of control subjects. The cleanliness of the sample (all unmedicated, very narrow age range, no other forms of traumatic exposure, high SES, minimal exposure to alcohol or drugs of abuse) might have compensated for that shortcoming, at least in part, by reducing error variance. Global analytic techniques, such as VBM, are limited by the need to adjust for multiple comparisons to minimize the risk of detecting chance-related differences. Consequently, only the most robust differences tend to emerge. We recently published results of an ROI analysis on these subjects and identified alterations in their hippocampus, corpus callosum, and frontal cortex (13). The focus of that paper was the identification of sensitive periods for effects of CSA on structures previously identified as susceptible.

These studies differ considerably from prior reports on the association between childhood abuse and brain morphometry. Previous studies recruited abused subjects meeting criteria for specific psychiatric disorders. This strategy is useful when the primary focus is on the neurobiology of the disorder. However, this strategy does not provide an unbiased perspective of the effects of exposure to childhood abuse. The alternative approach of selecting only subjects without psychopathology is equally problematic because it might underestimate the effects of exposure and confound consequences with preexisting morphometric differences that enhance resilience. The only way around this dilemma, in our opinion, was to recruit subjects with a history of exposure, regardless of psychiatric outcome. Including abused subjects with and without psychopathology avoids overestimating or underestimating consequences, and accepting virtually all types of outcomes eliminates concern that an identified abnormality was actually a preexisting risk factor for a specific disorder. Consequently, imaging differences observed in these subjects may generalize better to the population at large, as they are outcome independent.

Another unique feature of the present study is that these CSA subjects were unexposed to other forms of abuse or trauma. Prior studies included subjects who experienced different or multiple types of abuse (e.g., physical or sexual abuse) (2,5,8,70–72) or selected subjects exposed to CSA without excluding subjects who experienced multiple forms of abuse (3). Results from the present sample provide the only data available on the specific associations between CSA and brain structure and function. Such subjects are somewhat atypical (only one third of subjects reporting CSA) but are not rare (10% of the screened sample). Hence, this study may identify neurobiological differences that are specifically associated with exposure to CSA but may not apply to other forms of maltreatment.

This study was supported by ROI awards from the US National Institute of Mental Health (MH-53636, MH-66222) and National Institute of Drug Abuse (DA-016934, DA-017846) to MHT, and Grant-in-Aid for Scientific Research to AT from Japan-U.S. Brain Research Cooperation Program.

We thank Hanako Suzuki, Anthony Mullin, Kumiko Suzuki, Jordan Deifik, and Ray Fix for their assistance in data analysis and Cynthia McGreenery, Danielle Webster, and Dr. Carol A. Glod for recruitment and interviewing of subjects.

The authors report no biomedical financial interests or potential conflicts of interest.

1. Lange A, de Beurs E, Dolan C, Lachnit T, Sjollem S, Hanewald G (1999): Long-term effects of childhood sexual abuse: Objective and subjective characteristics of the abuse and psychopathology in later life. *J Nerv Ment Dis* 187:150–158.
2. Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, *et al.* (1997): Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. *Biol Psychiatry* 41:23–32.
3. Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B (1997): Hippocampal volume in women victimized by childhood sexual abuse. *Psychol Med* 27:951–959.
4. Driessen M, Herrmann J, Stahl K, Zwaan M, Meier S, Hill A, *et al.* (2000): Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Arch Gen Psychiatry* 57:1115–1122.
5. Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, *et al.* (2002): Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry* 159:2072–2080.
6. De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, *et al.* (1999): A.E. Bennett Research Award. Developmental traumatology. Part II: Brain development. *Biol Psychiatry* 45:1271–1284.
7. Teicher MH, Dumont NL, Ito Y, Vaituzis C, Giedd JN, Andersen SL (2004): Childhood neglect is associated with reduced corpus callosum area. *Biol Psychiatry* 56:80–85.
8. De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Beers SR, Hall J, *et al.* (2002): Brain structures in pediatric maltreatment-related posttraumatic stress disorder: A sociodemographically matched study. *Biol Psychiatry* 52:1066–1078.
9. Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, *et al.* (2001): Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. *Biol Psychiatry* 50:943–951.
10. De Bellis MD, Keshavan MS, Frustaci K, Shifflett H, Iyengar S, Beers SR, *et al.* (2002): Superior temporal gyrus volumes in maltreated children and adolescents with PTSD. *Biol Psychiatry* 51:544–552.
11. De Bellis MD, Keshavan MS, Spencer S, Hall J (2000): N-acetylaspartate concentration in the anterior cingulate of maltreated children and adolescents with PTSD. *Am J Psychiatry* 157:1175–1177.
12. Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM (2003): The neurobiological consequences of early stress and childhood maltreatment. *Neurosci Biobehav Rev* 27:33–44.
13. Andersen SL, Tomoda A, Vincow ES, Valente E, Polcari A, Teicher MH (2008): Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. *J Neuropsychiatry Clin Neurosci* 20:292–301.
14. Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP (2002): Developmental neurobiology of childhood stress and trauma. *Psychiatr Clin North Am* 25:397–426, vii–viii.
15. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, *et al.* (2002): Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci* 5:1242–1247.
16. Teicher MH, Samson JA, Polcari A, McGreenery CE (2006): Sticks, stones, and hurtful words: Relative effects of various forms of childhood maltreatment. *Am J Psychiatry* 163:993–1000.
17. Roy CA, Perry JC (2004): Instruments for the assessment of childhood trauma in adults. *J Nerv Ment Dis* 192:343–351.
18. First MB, Spitzer RL, Gibbon M, Williams JBW (1997): *Structured Clinical Interview for DSM-IV Axis I Disorders—Clinician Version (SCID-CV)*. Washington, DC: American Psychiatric Press.
19. Gunderson JG, Kolb JE, Austin V (1981): The diagnostic interview for borderline patients. *Am J Psychiatry* 138:896–903.
20. Steinberg M (1994): *Interviewer's Guide to the Structured Clinical Interview for DSM-IV Dissociative Disorder (SCID-D)*. Arlington, VA: American Psychiatric Publishing.
21. Orvaschel H, Puig-Antich J (1994): *Schedule for Affective Disorder and Schizophrenia for School-Age Children, Epidemiologic Version, Fifth Revision*. Fort Lauderdale, FL: Nova Southeastern University.
22. Williams JM (1991): *Memory Assessment Scales: Professional Manual*. Odessa, FL: Psychological Assessment Resources.
23. Navalta CP, Polcari A, Webster DM, Boghossian A, Teicher MH (2006): Effects of childhood sexual abuse on neuropsychological and cognitive function in college women. *J Neuropsychiatry Clin Neurosci* 18:45–53.

24. Hollingshead AB (1965): *Hollingshead Two Factor Index of Social Position, Occupational Categories*. Rockville, MD: National Institute of Health, Psychopharmacology Research Branch.
25. Ashburner J, Friston KJ (2000): Voxel-based morphometry—the methods. *Neuroimage* 11:805–821.
26. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001): A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14:21–36.
27. Good CD, Johnsrude I, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001): Cerebral asymmetry and the effects of sex and handedness on brain structure: A voxel-based morphometric analysis of 465 normal adult human brains. *Neuroimage* 14:685–700.
28. Okada T, Tanaka M, Kuratsune H, Watanabe Y, Sadato N (2004): Mechanisms underlying fatigue: A voxel-based morphometric study of chronic fatigue syndrome. *BMC Neurol* 4:14.
29. Ashburner J, Friston KJ (2005): Unified segmentation. *Neuroimage* 26:839–851.
30. Talairach J, Tournoux P (1988): *Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Medical Cerebral Imaging*. Stuttgart, Germany: Thieme.
31. Hayasaka S, Phan KL, Liberzon I, Worsley KJ, Nichols TE (2004): Nonstationary cluster-size inference with random field and permutation methods. *Neuroimage* 22:676–687.
32. Moorhead TW, Job DE, Spencer MD, Whalley HC, Johnstone EC, Lawrie SM (2005): Empirical comparison of maximal voxel and non-isotropic adjusted cluster extent results in a voxel-based morphometry study of comorbid learning disability with schizophrenia. *Neuroimage* 28:544–552.
33. Friston KJ, Holmes A, Poline JB, Price CJ, Frith CD (1996): Detecting activations in PET and fMRI: Levels of inference and power. *Neuroimage* 4:223–235.
34. Worsley KJ, Andermann M, Koulis T, MacDonald D, Evans AC (1999): Detecting changes in nonisotropic images. *Hum Brain Mapp* 8:98–101.
35. Bookstein FL (2001): “Voxel-based morphometry” should not be used with imperfectly registered images. *Neuroimage* 14:1454–1462.
36. Dale AM, Fischl B, Sereno MI (1999): Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 9:179–194.
37. Fischl B, Sereno MI, Dale AM (1999): Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage* 9:195–207.
38. Fischl B, Liu A, Dale AM (2001): Automated manifold surgery: Constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Trans Med Imaging* 20:70–80.
39. Fischl B, Sereno MI, Tootell RB, Dale AM (1999): High-resolution inter-subject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp* 8:272–284.
40. Fennema-Notestine C, Stein MB, Kennedy CM, Archibald SL, Jernigan TL (2002): Brain morphometry in female victims of intimate partner violence with and without posttraumatic stress disorder. *Biol Psychiatry* 52:1089–1101.
41. Hubel DH, Wiesel TN (1998): Early exploration of the visual cortex. *Neuron* 20:401–412.
42. Lewis TL, Maurer D (2005): Multiple sensitive periods in human visual development: Evidence from visually deprived children. *Dev Psychobiol* 46:163–183.
43. Garey LJ (1984): Structural development of the visual system of man. *Hum Neurobiol* 3:75–80.
44. Teicher MH, Tomoda A, Andersen SL (2006): Neurobiological consequences of early stress and childhood maltreatment: Are results from human and animal studies comparable? *Ann NY Acad Sci* 1071:313–323.
45. Choi J, Jeong B, Rohan ML, Polcari AM, Teicher MH (2009): Preliminary evidence for white matter tract abnormalities in young adults exposed to parental verbal abuse. *Biol Psychiatry* 65:227–234.
46. Knudsen EI (2004): Sensitive periods in the development of the brain and behavior. *J Cogn Neurosci* 16:1412–1425.
47. Teicher MH (2002): Scars that won't heal: The neurobiology of child abuse. *Sci Am* 286:68–75.
48. Sar V, Akyuz G, Kundakci T, Kiziltan E, Dogan O (2004): Childhood trauma, dissociation, and psychiatric comorbidity in patients with conversion disorder. *Am J Psychiatry* 161:2271–2276.
49. Chu JA, Frey LM, Ganzel BL, Matthews JA (1999): Memories of childhood abuse: Dissociation, amnesia, and corroboration. *Am J Psychiatry* 156:749–755.
50. Ouyang L, Fang X, Mercy J, Perou R, Grosse SD (2008): Attention-deficit/hyperactivity disorder symptoms and child maltreatment: A population-based study. *J Pediatr* 153:851–856.
51. Sergent J, Ohta S, MacDonald B (1992): Functional neuroanatomy of face and object processing. A positron emission tomography study. *Brain* 115(Pt 1):15–36.
52. Devlin JT, Jamison HL, Gonnerman LM, Matthews PM (2006): The role of the posterior fusiform gyrus in reading. *J Cogn Neurosci* 18:911–922.
53. Tyler LK, Stamatakis EA, Dick E, Bright P, Fletcher P, Moss H (2003): Objects and their actions: Evidence for a neurally distributed semantic system. *Neuroimage* 18:542–557.
54. Barrett NA, Large MM, Smith GL, Michie PT, Karayanidis F, Kavanagh DJ, *et al.* (2001): Human cortical processing of colour and pattern. *Hum Brain Mapp* 13:213–225.
55. Rossion B, Joyce CA, Cottrell GW, Tarr MJ (2003): Early lateralization and orientation tuning for face, word, and object processing in the visual cortex. *Neuroimage* 20:1609–1624.
56. Rossion B, Dricot L, Devolder A, Bodart JM, Crommelinck M, De Gelder B, *et al.* (2000): Hemispheric asymmetries for whole-based and part-based face processing in the human fusiform gyrus. *J Cogn Neurosci* 12:793–802.
57. Sugiura M, Kawashima R, Nakamura K, Okada K, Kato T, Nakamura A, *et al.* (2000): Passive and active recognition of one's own face. *Neuroimage* 11:36–48.
58. Druzgal TJ, D'Esposito M (2001): A neural network reflecting decisions about human faces. *Neuron* 32:947–955.
59. Domes G, Czeschnek D, Weidler F, Berger C, Fast K, Herpertz SC (2008): Recognition of facial affect in borderline personality disorder. *J Pers Disord* 22:135–147.
60. Fink GR, Halligan PW, Marshall JC, Frith CD, Frackowiak RS, Dolan RJ (1996): Where in the brain does visual attention select the forest and the trees? *Nature* 382:626–628.
61. Kiyosawa M, Inoue C, Kawasaki T, Tokoro T, Ishii K, Ohyama M, *et al.* (1996): Functional neuroanatomy of visual object naming: A PET study. *Graefes Arch Clin Exp Ophthalmol* 234:110–115.
62. Bischof M, Bassetti CL (2004): Total dream loss: A distinct neuropsychological dysfunction after bilateral PCA stroke. *Ann Neurol* 56:583–586.
63. Joo EY, Tae WS, Han SJ, Cho JW, Hong SB (2007): Reduced cerebral blood flow during wakefulness in obstructive sleep apnea-hypopnea syndrome. *Sleep* 30:1515–1520.
64. Joo EY, Seo DW, Tae WS, Hong SB (2008): Effect of modafinil on cerebral blood flow in narcolepsy patients. *Sleep* 31:868–873.
65. Krakow B, Sandoval D, Schrader R, Keuhne B, McBride L, Yau CL, *et al.* (2001): Treatment of chronic nightmares in adjudicated adolescent girls in a residential facility. *J Adolesc Health* 29:94–100.
66. Agargun MY, Kara H, Ozer OA, Selvi Y, Kiran U, Kiran S (2003): Nightmares and dissociative experiences: The key role of childhood traumatic events. *Psychiatry Clin Neurosci* 57:139–145.
67. Noll JG, Trickett PK, Susman EJ, Putnam FW (2006): Sleep disturbances and childhood sexual abuse. *J Pediatr Psychol* 31:469–480.
68. Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, *et al.* (2001): Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. *Biol Psychiatry* 50:943–951.
69. Carrion VG, Weems CF, Reiss AL (2007): Stress predicts brain changes in children: A pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. *Pediatrics* 119:509–516.
70. De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, *et al.* (1999): Developmental traumatology. Part II: Brain development. *Biol Psychiatry* 45:1271–1284.
71. Vermetten E, Schmahl C, Lindner S, Loewenstein RJ, Bremner JD (2006): Hippocampal and amygdalar volumes in dissociative identity disorder. *Am J Psychiatry* 163:630–636.
72. Jackowski AP, Douglas-Palumberi H, Jackowski M, Win L, Schultz RT, Staib LW, *et al.* (2008): Corpus callosum in maltreated children with posttraumatic stress disorder: A diffusion tensor imaging study. *Psychiatry Res* 162:256–261.