RUNNING HEAD: NEUROBIOLOGY OF PHYSICAL ABUSE

# Child maltreatment is associated with alterations in the orbitofrontal cortex: A tensor-based morphometry investigation of brain structure and behavioral risk

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**Individuals who experience physical abuse during childhood are at heightened risk for a broad array of social and health difficulties. However, little is known about how this behavioral risk is instantiated in the brain. Here we examine a neurobiological contribution to individual differences in human behavior using a novel approach to quantification of brain development appropriate for use with pediatric populations paired with an in-depth measure of social behavior. We show that alterations in the orbitofrontal cortex among individuals who experienced physical abuse are related to social difficulties. These data suggest a biological mechanism linking early social learning to later behavioral outcomes. In addition, involvement of the orbitofrontal cortex may explain why many of the behavioral problems associated with child abuse do not emerge until adolescence or early adulthood.**

Maltreatment of children by the adults who should be providing nurturance and protection is increasingly common. For example, the United States and the United Kingdom each confirm nearly a million victims of domestic child abuse and neglect every year[1,2]. It has been well documented that children who are maltreated early in life are at heightened risk for a variety of behavioral, social, and health problems throughout their lives[3]. The occurrence of child maltreatment is a humanitarian tragedy, but the phenomenon also raises complex issues about human developmental biology. This represents the classic problem of how early experiences influence the nature and trajectory of brain development. Here we examine the effects of early adverse parental care on a brain system responsible for regulation of social behavior in human children.

Despite documentation of the broad range of difficulties observed among individuals who experienced early child abuse, little is understood about the neurobiological mechanisms that underlie the problems that emerge years or even decades following early child maltreatment, issues that span from low educational achievement to behavioral problems to poor health[4]. The orbitofrontal cortex (oFC) is a key component of a brain circuit that governs emotion and social regulation[5,6] and when disrupted, confers an increased vulnerability for the development of mental health problems such as depression or substance abuse[7,8]. Functional neuroimaging studies point to this orbital sector of the prefrontal cortex as supporting behaviors such as inhibition, appropriate responses to other people's moods, and self-regulation of social–emotional behavior[9,10]. This brain region supports the monitoring of behavioral outcomes[11] and regulation of affective states[12,13,14] -- domains of behavior frequently affected in children who have been physically abused[15].

Maltreated children's home environments are marked by high levels of stress, but the neurobiological mechanisms affected by this type of early environment is not well understood[16]. We focused our examination on development of the oFC in previously maltreated children because the extensive anatomical connections of the oFC may help account for the diverse range of behavioral sequelae observed in this population. All sensory modalities project to the oFC, conveying highly processed information from the external environment[11]. The amygdala, entorhinal and perirhinal cortices, along with the hypothalamus, thalamus, brain stem, caudate and the ventral tegmental area all connect with the oFC, allowing for direct and indirect influence and control of emotional behaviors[17]. From a developmental perspective, growth of the oFC is still not fully understood. Basic performance of tasks linked to the oFC begin to emerge

around 30 months of age in children; yet performance on other tasks mediated by the oFC show drastic changes between puberty and early adulthood[18,19]. Longitudinal neuroimaging studies suggest that the oFC is one of the last regions in the brain to fully develop in humans[20], with changes in the oFC seen until 20 years of age or later. We reasoned that because the oFC has a protracted period of post-natal development, this region is especially likely to be vulnerable to the effects of early adverse post-natal experiences. Indeed, non-human animal models suggest that early stress is associated with alterations in portions of the prefrontal cortex (PFC)[21]. As an example, infant rodents had lower spine densities and shorter apical dendrites in the orbitofrontal cortex when separated from one of their parents[22]. Similar alterations in the PFC have also been noted in rhesus macaques, separated in infancy from their mothers at 2 months of age, with decreases noted in white matter in the PFC compared to control-comparison monkeys[23]. Importantly, early dysfunction of the oFC may not become apparent until adolescence or early adulthood, when this brain region becomes fully functional[9]. This may account for why some behavioral problems in previously maltreated individuals do not manifest in early childhood.

We assessed the relationship between development of the oFC and the social functioning of children who were verified victims of physical abuse. To do so, we used a novel analytic approach that is especially applicable to evaluating volumetric variations among pediatric samples: a Tensor-Based Morphometry (TBM) framework[24,25]. TBM uses the Jacobian determinant of the deformation field that is required to register one brain to another to detect volumetric changes. This procedure is especially powerful for addressing limitations posed in neuroimaging studies of pediatric brains. Importantly, we also evaluated and controlled for pubertal stage in assessing brain development. Pubertal timing is affected by early adversity[26],

has been associated with increased risk for health and psychosocial outcomes[27], may affect brain development[28,29,] and is therefore an important variables to control for in maltreated populations. We hypothesized that the orbitofrontal cortex would be smaller in children who had experienced prolonged maltreatment and, since this region is important for behavioral and emotional flexibility, these alterations would be predictive of children's adaptive social behavior. To test this hypothesis we assessed each child's competence in stress-regulation across numerous social domains, both indexing the objective impact of stressful events as well as the child's subjective experience of the event.

## Results

### *Brain Measurements*

As hypothesized, one of the largest differences between abused and nonabused children was in the right oFC, where those who had experienced physical abuse had smaller brain volumes (extent=1.925 cubic centimetres, $p<.001$ corrected, peak t in cluster = 3.93). To ensure specificity of this result, this finding is corrected for individual differences in the overall sizes of children's brains (whole-brain volume) and each child's pubertal status. Tables 1 and 2 report other brain regions where victims of abuse differed from controls.

### *Social Functioning*

Children who had been the victims of physical abuse reported more stressors in their academic (Typically-Developing: 1.6829 +/- 0.6869; Physically-Abused: 2.9032 +/- 1.075634346; $F = 34.338$, $p<.001$), behavioral (Typically-Developing: 1.5609 +/- 0. 6818; Physically-Abused: 2.6290+/- 1.0244; $F = 28.146$, $p<.001$), peer (Typically-Developing: 2.1097 +/- 0.8102;

Physically-Abused: 2.9839 +/- 0.8214; F = 20.305, p<.001), and family (Typically-Developing: 2.1829 +/- 0.7886; Physically-Abused: 3.1935 +/- 0.8914; F = 25.907, p<.001) domains (see Fig. 1). Though the LSI probes both subjective and objective aspects of stress, these differences are regarding objective, yet contextually relevant indices of chronic stress.

*Relationship between Brain Structure and Social Functioning*

To examine relationships between the oFC development and children's behavioral functioning, we used logical and conjunction analyses to investigate whether a particular brain area that is different between groups is also the same area that is related to behavioral variables within the physically abused group alone[30]. This approach is described under *Statistical Analyses*, below. As hypothesized, smaller volumes in the right oFC observed in the physically abused children predicted problems in children's functioning (all regions, $p < .000025$, uncorrected). The partial correlation between oFC volume and the family stress scale was $r = -.516$, $p = .004$. Greater difficulties in the child-parent relationship, such as more frequent arguments and less emotional support, were associated with smaller oFC volumes (see Fig. 2a). The partial correlation between oFC volume and children's experience of academic problems/school stress was $r = -.504$, $p = .005$ (see Fig. 2b). Greater academic difficulties, such as failure of 3 or more subjects in 1 year and full-time placement in a learning disabilities class, were associated with smaller oFC volumes. Both of these correlations controlled for variation between individual children in whole-brain volume and pubertal status. Relationships between other brain regions and children's social functioning are detailed in the *Supplementary Material*.

**Discussion**

Our findings indicate that oFC volumes are smaller in children who have suffered early aberrant parental care in the form of physical abuse, and that these volumetric alterations are associated with difficulties children experience in various aspects of their social lives. The oFC is a key component of a circuit that aids in adaptation to changing environmental contingencies and plays an important role in the control of emotion and motivational states. The structural alterations that we observed in abused childrens' oFC may lead to functional difficulties for these children, compromising their abilities to navigate in and adaptively regulate to changing social contexts.

The data reported here are consistent with studies of rodents and primates that indicate that early stress affects development of the PFC[31]. Moreover, previous research examining neurological-damaged patients with oFC lesions indicate that damage to this brain region has been linked with deficits in emotion, mood, and social regulation[5]. Although previous neuroimaging investigations have noted structural brain differences among maltreated children[32,33,34,35], extant studies have not found robust connections between brain and behavior. This may be due to the fact that previous studies have tested very heterogeneous samples of children—for example, those who experienced maltreatment but who also had concurrent psychiatric conditions such as post-traumatic stress disorder (PTSD), or samples of children with a wide range of different adverse childhood experiences including histories of sexual abuse, physical abuse, emotional abuse, and/or neglect. To address these issues, we focused on one specific form of maltreatment, did not select research participants on the basis of psychopathology, and assessed pubertal status—a likely source of variation among individual children that influences brain growth[25].

Another challenge faced by previous investigations is that children's brains are difficult to measure. Methodologically, our study design employed a TBM approach, with information generated from a novel registration algorithm (Symmetric normalization; SyN[36]). In a recent comparison of 14 non-linear registration algorithms, SyN emerged as one of the best available warping algorithms[37]. This approach represents an important advance because other analytic approaches for structural imaging data, such as parcellation or voxel-based morphometry, may especially limit studies of children's brain development. Parcellation divides the brain into large zones, but in doing so, aggregates functionally divergent brain regions together, each of which may be differentially involved in behavioral outcomes[38]. Voxel-based morphometry, a commonly used approach, may be less reliable with pediatric populations because of the use of adult anatomical templates and spatial normalization parameters[39,40]. The approach we employ here minimizes these sources of variability (e.g., brain tissue segmentation), utilizes a study-specific anatomical template and yields high sensitivity at the voxel level.

By specifically linking child maltreatment to focal neuroanatomical alterations and those alterations to behavioral changes, our results suggest one potential mechanism, structural changes in the oFC, through which child maltreatment may put individuals at greater risk for a variety of behavioral problems throughout their lives. Further study is needed to more fully understand the brain-behavior effects of early post-natal social experience. One limitation of our design is that the results are based upon one time point, therefore we cannot discern whether oFC development is slowed or significantly delayed. For this reason, we refer to "differences" or "alterations" in the describing our findings. As a next step, functional neuroimaging, in conjunction with anatomical measurement, may be used to examine how structural variation in

the oFC might be related to variations in functional connectivity between the oFC and other brain regions that convey behavioral risk from child abuse. Arnsten[31] theorized that chronic stress, such as maltreatment, may weaken the regulatory abilities of structures that provide negative feedback on the stress response (such as the PFC), but also bolster the structures that promote the stress response, such as the amygdala. To date, there is little known about molecular stress-signaling mechanisms likely to be related to morphological alterations of the PFC; one candidate might be alterations of catecholamine pathways and increasing noradrenergic innervation of the PFC leading to higher levels of phosphatidylinositol–protein kinase C and cyclic adenosine monophosphate signaling[31]. Preliminary research[41] has found alterations in catecholamine excretion in a small sample of abused girls, providing initial support for alterations in this stress-signaling cascade. Future studies could combine these types of physiological metrics with structural neuroimaging using a design similar to the one employed here.

Overall, children who were victims of physical abuse had alterations in oFC and these alterations were related to functioning in different domains of behavior. This finding suggests a potential neurobiological mechanism through which early adverse experiences constitute risks for children's cognitive and emotional development.

## Methods

### Participants

Seventy-two children (31 physically abused, 41 nonabused) participated in this study. Physically abused children and their families were recruited by letters forwarded by the Department of

Human Services in Dane County, WI, to families with substantiated cases of physical maltreatment. Nonabused children were recruited from the Madison community by posting fliers. Parents completed the Parent–Child Conflict Tactics Scale (PC-CTS)[42], a 20-item measure of the frequency with which a parent has carried out specific acts of physical aggression toward the child. To qualify as controls in the present study, children were required to have scores below 12 on the PC-CTS. Children whose parents scored at least 20 on the physical abuse subscale on the PC-CTS and/or had substantiated cases of physical abuse on record with the Dane County Department of Human Services were classified as abused.

Groups were similar on demographic variables (for additional information, see Supplemental Materials). Whole-brain volume (Physically-Abused: 1387.57 +134.26 cubic centimeters; Typically-Developing: 1466.98 +121.09 cubic centimeters; F=6.91; p=.011) was different between groups, with physically-abused subjects have smaller overall volumes. All children completed a physical exam with Tanner's staging[43,44]. There was a trend for a group difference in pubertal-status (Physically-Abused: 1.758 +/-1.0791; Typically-Developing: 1.354 +/-1.1401; F=2.325, p=.132). Marshall and Tanner[43,44] described five stages of puberty, ranging from 1 (no development) to 5 (adult development).

Interview Methods

To assess psychological functioning, parents and children each separately completed the Life-Stress Interview (LSI)[45]. This semi-structured interview assessed stressful life events of both chronic and episodic nature. Children were interviewed regarding stressors in domains relevant to their lives, e.g., school, peer, and family. Parents were also asked about their child's

functioning within these various domains. Advanced graduate students, staff and/or postdoctoral fellows in psychology conducted all interviews. The trained panel of between 3 to 6 people then scored impact ratings for each life event based on parent's and child's separate reports on a 5-point scale (1–5, from no or minimal impact to severe impact), which were developed by Rudolph and Hammen[45]. Once parent and child reports were scored individually, a consensual report was made regarding the child by integrating information from both informants. Increasing scores are related to more serious difficulties in each subdomain. For example, a score of 1 on the academic subscale is demonstrative of a child getting mostly A's and doing above average work, while a score of 5 would be given with the failure of 3 or more subjects in 1 year and full-time placement in a learning disabilities class. Interviewers received intensive training from the developers (of the LSI) at the University of Illinois at Urbana-Champaign. High reliability has previously been achieved for the interviews classification of stressful life events (intra-class correlation coefficients of .85) [45,46].

MRI Acquisition

All children completed one MRI scan. High-resolution anatomical MRI images were obtained using a 3-Tesla GE SIGNA (General Electric Medical Systems, Waukesha, WI) scanner with a quadrature head RF coil. A three-dimensional, inversion recovery (IR) pulse sequence was used to generate T1-weighted images with the following parameters: TR/TE = 21/8 ms, flip angle = 308, 240 mm field of view, 256-192 in-plane acquisition matrix (interpolated on the scanner to 256-256), and 128 axial slices (1.2 mm thick) covering the whole brain. Before MRI scanning, participants were oriented to the MRI through the use of a mock-MRI simulator. During MRI

acquisition, participants were instructed to stay as still as possible and were able to watch a movie of their choosing.

Imaging Processing and Template creation

T1-weighted images were reconstructed and masked to include brain tissue and ventricular cerebral spinal fluid. These masked images were then used to construct an optimal, population-specific template, using a diffeomorphic shape and intensity averaging technique[36],[47]. This processing yielded an unbiased average shape and appearance template, as well as the set of diffeomorphisms and inverse diffeomorphisms that map from template to each individual. For additional details, see Supplementary Materials.

*Symmetric diffeomorphic image normalization and Tensor-based morphometry*

After going through a 6-parameter rigid-body transformation, each individual brain was registered to our template using SyN. This algorithm allows for large deformations, but also constrains the deformations to be physically reasonable. The nonlinear transformations resulting from the SyN algorithm also provide deformation tensor fields, defined in the optimal template space, that describe the voxel-wise shape change from the template to each subject's brain. Jacobian determinants of the deformation field indicate the fractional volume expansion and contraction at each voxel, quantifying the magnitude of regional volume alterations required to match the template. Before the statistical testing, this adjusted Jacobian map was subjected to a log transformation to make the distribution closer to the normal distribution[36]. Jacobian determinants were then smoothed with a 4mm Full-Width, Half Max Gaussian Filter via

Statistical Parametric Mapping (Wellcome Trust Centre for Neuroimaging, University College London).

*Statistical Analysis*

Voxel-wise group t-tests and whole brain regressions were next conducted in FMRISTAT[48]. Whole-brain volume and pubertal status were entered into linear regression model as nuisance variables. An initial statistical threshold of $t(68)=2.6503$, $p=.005$ uncorrected, was used in examining any possible brain differences. Signal above this threshold was then corrected using Gaussian Random-Field Theory[49] to limit Type I error. Using this approach, regions needed to have a peak $t>2.6503$ and an extent>284 voxels, which was equivalent to $p\leq.05$ corrected.

In addition to examining group differences, voxel-wise correlations were also conducted with scores from the LSI subscales. These analyses were only conducted within the abused samples, as significant group differences were detected on all of the LSI subscales (see Supplemental Materials). These correlations were then used in a logical AND conjunction analysis to identify the brain regions that were different between groups and also related to functioning for the physically-abused sample in various domains as assessed by the LSI. This analytical approach has been employed in a number of research studies[50]; such an approach is a straightforward way to find brain regions different between groups and also correlated with behavioral outcomes, with minimal statistics.

Group differences and correlation with the LSI were both thresholded at $p=.005$, uncorrected (e.g., LSI correlation threshold $t(29)=3.047$) and combined to see any overlapping regions. Brain

group differences from the first step of our analyses at p=.05 corrected were used to mask these logical AND conjunction analyses. In addition, a minimum cluster-threshold of 5 voxels or greater was set for all logical AND conjunctions to further minimize false-positives. Assuming independence of this test, these results are significant at 0.000025, (.005*.005), uncorrected. The peak coordinates for all analyses were mapped to MNI space by registering the custom template to the MNI152 Average Template (Montreal Neurological Institute, Montreal, Canada) as presented in Tables 1 and 2, (along with Supplementary Table 1) to allow comparison from other studies.

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**Author Contributions**

JLH, SDP, and RJD designed the study; JLH, MKC, BBA, and JCG processed the neuroimaging data; EAS collected and scored the interview data; JLH, SDP, and RJD wrote the manuscript.

Table 1.

*Brain Regions: PA<Control*

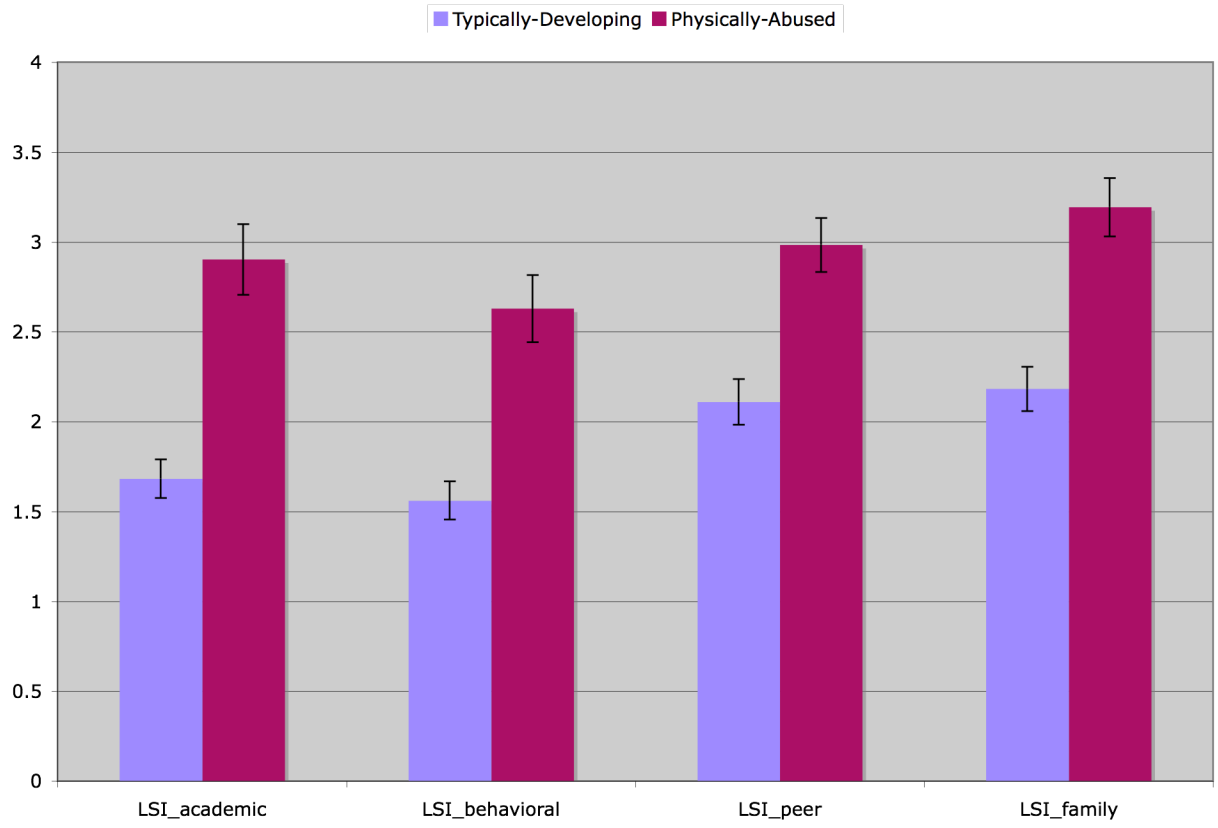
| Brain Area | Cluster Size (in 1mm voxels) | p-value (corrected via random field theory) | Peak within Cluster | Approximate Coordinates in MNI space (x, y, z) |
|---|---|---|---|---|
| Right Middle Temporal Lobe | 2129 | p<.001 | 5.18 | +54, -8, +18 |
| Right orbitofrontal Cortex | 1925 | p<.001 | 3.93 | +34, +35, -8 |
| Right Inferior Temporal Lobe / Temporal Pole | 1442 | p<.001 | 4.5 | +49, +7, -26 |
| Bilateral Thalamus | 1354 | p<.001 | 5.55 | -4, -9, +5 |
| Right Parietal Lobe | 1108 | p<.001 | 4.44 | +51, -27, +25 |
| Right Posterior Parietal Lobe | 894 | p<.001 | 3.54 | +30, -56, +38 |
| Right Dorsolateral PFC | 634 | p<.001 | 4.06 | +16, +52, -42 |
| Right ventral-medial PFC | 626 | p<.001 | 4.18 | +10, +53, -22 |
| Right Inferior Temporal Lobe / Temporal Pole | 576 | p<.001 | 3.99 | +33, +14, -38 |
| Left Inferior Temporal Lobe / Temporal Pole | 555 | p<.001 | 3.99 | -36, +7, -36 |

| | | | | |
|---|---|---|---|---|
| Left Superior Frontal Lobe | 499 | p=.001 | 4.22 | -22, -1, +68 |
| Right Frontal Cortex | 442 | p=.002 | 3.68 | +59, +9, +32 |
| Left Dorsolateral PFC | 407 | p=.004 | 3.51 | -16, +42, +45 |
| Left Middle Temporal Gyrus | 368 | p=.009 | 3.46 | -63, -18, -19 |
| Left Parietal Cortex | 342 | p=.015 | 3.94 | -49, -31, +14 |
| Right Superior Temporal | 335 | p=.017 | 3.26 | +49, -28, +2 |
| Left Vermis | 316 | p=.025 | 3.61 | -6, -67, -43 |
| Left Postcentral | 286 | p=.045 | 4.22 | -59, -22, +46 |

Table 2.
*Brain Regions: PA>Control*

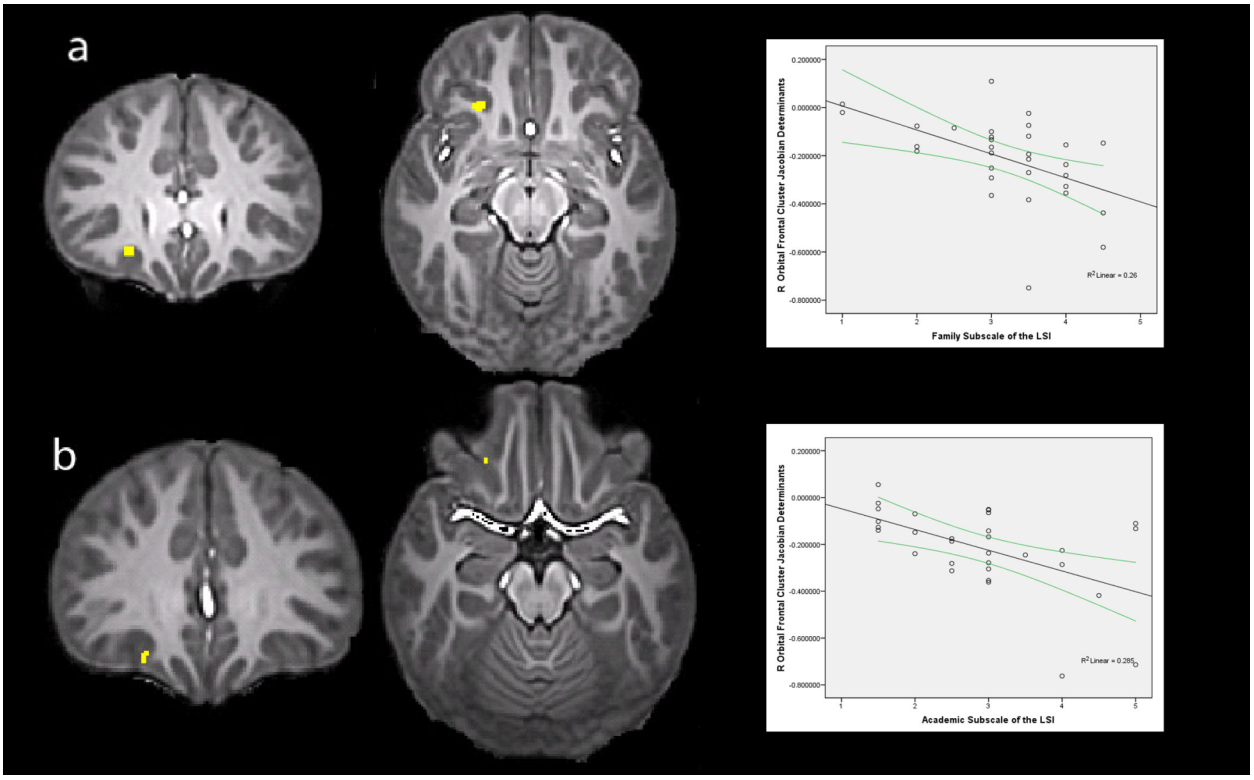
| Brain Area | Cluster Size (in 1mm voxels) | p-value (corrected via random field theory) | Peak within Cluster | Approximate Coordinates in MNI space (x, y, z) |
|---|---|---|---|---|
| Right Occipital Lobe | 2347 | p<.001 | 4.93 | +39, -82, +30 |
| Right Cingulate | 586 | p<.001 | 4.07 | +4, -17, +51 |
| Left Cerebellar White Matter | 557 | p<.001 | 5.25 | -26, -38, -42 |
| Left Frontal White Matter | 479 | p=.001 | 4.89 | -17, +39, +28 |
| Left Lateral Cerebellum | 306 | p=.003 | 3.83 | -47, -48, -30 |
| Right Cerebellum White Matter | 296 | p=.037 | 3.35 | +26, -53, -36 |
| | | | | |

*Figure 1.*
*Results from LSI subscales for Non-maltreated Control and Physically-Abused Adoles*




Caption: Figure 1 shows Children who had been the victims of physical abuse reported more stressors in their academic, behavioral, peer, and family domains ($p<.001$ for each domain).

*Figure 2.*
Logical AND Conjunction Analyses for the oFC




Caption: Figure 2 shows results of Logical and conjunction for the oFC. The top panel (a) shows the oFC cluster that was smaller in physically abused children compared to controls and that there is a significant negative relationship between oFC development and the occurrence of family stress. The bottom panel (b) shows the oFC cluster that was smaller in physically abused subjects compared to controls and shows a significant negative relationship between oFC development and school-related stress. For both clusters, smaller volumes (mean Jacobian determinants shown on the ordinate of each scatterplot**)** were related to increasing difficultly in social functioning, both clusters, p<. 000025, uncorrected. These analyses are corrected for individual differences in whole brain volume and pubertal status.

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# Supplemental materials

## Methods

### Pubertal Exam

Experienced pediatric nurse practitioners were trained to conduct physical exams for research purposes by Ronald Dahl, M.D. Pediatric nurse practitioners inspected breast development with brief palpation for girls, and visually examined pubic hair. An orchidometer was used to measure testicular size in boys[51] along with visual inspection of genitals and pubic hair. Inter-observer reliability between the nurse practitioners (N=10) was good, $\kappa$=0.88.

### Life-Stress Interview

The LSI is a semi-structured interview, which assessed stressful life events of both chronic and episodic nature. After interviewing both parent and child, the interviewer and a panel of independent raters then reviewed these reports. Each raters did not participate in interviewing that individual participant. Chronic stress was defined as on-going stressful conditions with duration of one month or longer. Interviews assessed such stress in each life domain (e.g., school stressors, peer relationships, and family relationships) with multiple probing questions. To assay episodic stress, children and parents were asked to freely recall stressful events that had occurred in the past year (i.e., 'has anything happened that has upset you or caused you trouble, or have there been any big changes in your family or in your life?'). Specific inquiries were also made about particular life events within each domain. For both chronic and episodic stress, interviewers took notes regarding the specific events and stressful conditions present in children's lives reported by both parents and children. The family subscale, for example,

evaluates on the basis of parent time availability, trust, emotional support, and conflict resolution between parent and child. A score of 1 is given when a child has an exceptionally quality relationship with both parents, while a score of 5 is given when a child has very poor relationships with parents, lack of communication, frequent arguments, and anger persistent after arguments over between parent and child.

The ratings of episodic stress between parent and child varied slightly across domain, but were significantly correlated, with r-values >.57 and p-values <.001 (LSI-academic r=.803, p<.001; LSI-behavioral r=.639, p<.001; LSI-peer r=.573, p<.001; LSI-family r=.698, p<.001).

Imaging Processing and Template creation

T1-weighted image were reconstructed via Analysis of Functional NeuroImages[52], converted to ANALYZE format, and corrected for field inhomogenity via N3[53]. Whole brain masks were then drawn by hand via the BrainMaker module in the Spect, Pet, and MRI analysis software (SPAMALIZE; http://brainimaging.waisman.wisc.edu/~oakes/spam/spam_frames.htm). These masks. All other extraneous aspects of the brain (e.g., dura matter, skull) were excluded. These images were then used in template creation.

The MRI template was study-specific, constructed based on all subjects, containing children who had suffered maltreatment and children who had not suffered such adverse early stress. Template construction consisted of a multi-resolution strategy (for this study, a four level Gaussian pyramid) as well as the similarity metric for the optimization, along with a maximum number of iterations. We used the region-based cross-correlation similarity metric, which is optimal in

dealing with locally varying inhomogeneity in the appearance of images. The maximum number of iterations in the normalization was set to 200, although convergence may occur before the maximum is reached

## Results

### *Brain Measurements*

Compared with non-maltreated control subjects, subjects who had been victims of physical abuse showed volume alterations in numerous areas throughout the brain. Table 1 (in the main body of this report) details regions where significantly smaller volumes were found in children who had been victims of abuse. In brief, smaller volumes in physically-abused subjects were noted in the Right Temporal, Right Frontal, and Bilateral Parietal Lobes. Within the right temporal lobe, the greatest differences were noted in the middle and inferior portions, while in the frontal lobe, large changes were noted in the orbital frontal and dorsolateral-prefrontal cortices. Additionally, major alterations were noted bilaterally in the thalamus, with the greatest difference in the left thalamus. Table 2 (in the main body of this article) reports the brain regions where significant larger volumes for physically abused children (as compared to typically-developing non-maltreated children) were noted. Larger volumes for physically-abused subjects were specifically found in the right posterior cingulate and in white matter in the cerebellum and prefrontal cortex. Additionally, major alterations were noted in Occipital Lobe. All of these alterations take into account variation in whole-brain volume and pubertal status.

*Relationships between Brain Structures and Life Stress*

For the academic subscale, the smaller volumes in Left Parietal Lobe and Right Temporal Lobe seen initially in physically abused children displayed a significant negative relationship with functioning, with smaller volumes seen with increasing problems in this domain. Larger volumes for the physically abused sample in the Right Cingulate displayed a significant positive relationship with functioning in the academic domain, with larger volumes seen with greater functional impairments. In the Behavioral domain, larger white matter volumes in left PFC were positively correlated with functioning in the broad behavioral domain as assessed by the Life-Stress Interview with greater volumes in the brain region related to increasing problems. No brain regions survived the logical conjunction of whole-brain correlation with the peer subscale of the LSI AND brain differences significant different between physically abused and control subjects.

**Discussion**

When employing DBM, we see significant differences across the brain in numerous important brain regions. We see larger volumes in prefrontal white matter, which may reflect abnormalities in white matter, such as edema. Interestingly, similar abnormalities have been reported in psychopathologies where emotional regulation is aberrant[54].

Supplementary Table 1.

*Additional Results from Logical AND Conjunction Analyses*

| Brain Area | Logical AND Conjunction of | Cluster Size (in 1mm voxels) | Approximate Coordinates in MNI space (x, y, z) |
|---|---|---|---|
| Left Parietal Lobe | PA<Control Group Brain Differences AND Negative Correlation LSI Academic | 34 | -58, -22, +44 |
| Right Temporal Lobe | PA<Control Group Brain Differences AND Negative Correlation LSI Academic | 14 | +51, -30, +1 |
| Right Cingulate | PA>Control Group Brain Differences AND Positive Correlation LSI Academic | 7 | +88, +107, +123 |
| Left Prefrontal White Matter | PA>Control Group Brain Differences AND Positive Correlation LSI Behavioral | 15 | +104, +169, +99 |
| | | | |

p-value for all clusters, p<. 000025, uncorrected

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